

## Gynaecological cancer and night shift work: A systematic review

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### ABSTRACT

Night shift work can affect hormonal balance, and so might be a risk factor for gynaecological malignancies. This report presents a systematic review on the association between this occupational exposure and the incidence of gynaecological cancers other than breast cancer. We searched for original articles addressing this issue in PubMed/MEDLINE, EMBASE and Web of Science, and used the Newcastle–Ottawa Quality Index to evaluate the methodological quality of those reports selected for review. Globally, we found only six articles, which provided the results of just six research studies: four examined ovarian cancer, two endometrial tumours and two cervical cancer. Our results show that this matter has received scant attention from the research community, and that the little evidence available does not show any clear relationship between night shift work and ovarian, endometrial or cervical cancer. More prospective rigorous studies are needed to evaluate these associations.

### 1. Introduction

Night shift work (NSW) has awakened a growing interest in the research community in the last decade, and its prevalence is increasing. According to the data collected in the sixth EU Survey on Working Conditions in 2015, 14% of the female working population reported working during the night [1]. In 2007, the International Agency for Research on Cancer (IARC), based on strong animal and limited human evidence, concluded that NSW that involves circadian disruption was probably carcinogenic for breast cancer [2]. The most commonly alleged pathway focuses on the effect of the lower melatonin levels caused by exposure to light at night [3,4]. Available information suggests that this hormone may be involved in the regulation of gonadal function by influencing the hypothalamic-pituitary-gonadal axis [5], and it is noteworthy that night shift workers seem to have increased levels of sex hormones [6,7]. Therefore, other hormone-dependent tumours could also be related to NSW [8]. Among female cancers, ovarian, endometrial and cervical cancer represent a significant burden for women, and all together account for more than 220.000 new cases per year according to IARC [9]. Our aim is to summarize the existing evidence on the relationship between NSW and gynaecological tumours

by performing a systematic review conducted according to the PRISMA and MOOSE guidelines [10–13].

### 2. Methods

#### 2.1. Data sources, search strategy, eligibility criteria and study selection

We aimed to select all observational studies providing original data that included NSW – defined as night-time work or shift work in hours covering midnight- as risk exposure and gynaecological cancer incidence and/or mortality as outcome. For this purpose, we searched for original articles in PubMed/MEDLINE (<http://www.ncbi.nlm.nih.gov/pubmed/>), EMBASE (<http://www.embase.com/home>), and in the Web of Science (WOS) published until august of 2017, using the terms (nightshift OR “night shift” OR shiftwork OR “shift work” OR night-work) combined with - “cancer” and the corresponding tumour site (i.e. “ovarian”, “endometrial”, “uterine”, “cervical”, “fallopian” or “vulvar”). We only took into consideration results in English, Spanish, German or French. This approach was complemented by a manual search based on the references cited in the papers initially identified.

*Abbreviations:* NSW, night shift work; IARC, International Agency for Research on Cancer; OCA, oral contraception; HRT, hormonal replacement therapy; BMI, body mass index; NHS, nurse health studies; JEM, job-industry exposure matrix; JACC, Japan Collaborative Cohort Study; SIR, standardized incidence ratio; NOS, Newcastle-Ottawa index scale

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2.2. Data extraction & quality of studies assessment

Two independent members of our research team performed the abstract/title screening and the full text revision of those reports that addressed our topic of interest. In case of disagreement, a third author’s opinion allowed to achieve consensus. Afterwards, they extracted the information of the selected studies using a predefined data collection form. We also evaluated each study using the Newcastle-Ottawa Quality Index [14], a 8-item scale developed to assess the quality of non-randomised studies for meta-analyses with a maximum punctuation of nine stars. It assigns 4 stars to items related to selection and representativeness of the study groups. Another 3 stars correspond to items that evaluate the ascertainment of the exposure or the outcome of interest for case-control or cohort studies respectively. Finally, the remaining 2 points evaluate comparability of the groups in terms of control for potential confounders. In this regard, we defined a minimum (one star) and a preferred (second star) set of confounders to be considered per site location. In ovarian cancer [15], we assigned one star to those studies that adjusted by age, family history, menopausal status, parity, oral contraception (OCA), hormonal replacement therapy (HRT), and body mass index (BMI). The second star was awarded to those including at least four of the following: breastfeeding, age at menarche, age at menopause, hysterectomy, tubal ligation, smoking, diet and physical exercise, exposure to asbestos or perianal use of talcum powder. For endometrial cancer, our minimum set was age, BMI, OCA, menopausal status, parity and unspecified HRT; for the second star studies should additionally control for at least three of the following: unopposed exposure to oestrogens in HRT, polycystic ovarian syndrome, infertility, breastfeeding, age at menarche or menopause [16–19]. Finally, in cervical cancer the criteria for one star was adjusting at least by age, parity and smoking and, for the second star, at least three of the following: sexual behaviour, screening participation, other sexually transmitted diseases, immunodeficiency, vaccination status and family history [20].

3. Results

3.1. Search results

Fig. 1 summarizes the search results for NSW and risk of ovarian,

endometrial and cervical tumours. For ovarian cancer, we retrieved 50 records, including two added by manual search; after title and abstract screening and full text revision, four articles were included in this review [21–24]. Regarding endometrial cancer, our search yielded 53 results, with two additional papers found by manual search. In this case, two of the three articles selected for full text revision were considered in this report [24,25]. For cervical cancer, the bibliographic search found 19 results and the manual search recovered two reports. Again, only two papers fulfilled the inclusion criteria and were incorporated in this review [24,26]. One of them did not include material and methods [26], and was partially complemented with information from other papers of the same study[27–29]. Finally, our search did not find any paper focused on NSW and incidence/mortality of vulvar or vaginal cancer.

Overall, we found six reports from six research studies about the relationship between NSW and any gynaecological tumour. Most of them – one case-control [21] and three cohorts [22,23,25]- were carried out in the USA, another cohort study in Sweden [24], and the last one in Japan [26]. Table 1 lists these studies and shows their evaluation according to the quality assessment with Newcastle-Ottawa Scale (NOS). Nurse Health cohort Studies (NHS) I & II had the highest score, obtaining 8 out of 9 stars; they were only penalized for their focus on a single occupation. In contrast, the Japan Collaborative Cohort Study for Evaluation of Cancer, insufficiently described, only got 4 stars, in spite of our effort to look for complementary information. Table 2 summarizes the main characteristics and results of each report.

3.2. Ovarian cancer

We identified four reports – five studies- that provided risk estimates on the association between ovarian cancer and NSW: one case-control study [21] as well as NHS I & II and Schwarzbaum cohort studies [23,24] were focused on cancer incidence and the other one, American Cancer Prevention cohort study, studied fatal ovarian cancer [22].

The case-control study was conducted in the USA (Western Washington State) [21]. In this research, Bhatti et al. recruited, interviewed and studied a) 1101 women with invasive ovarian cancer and 394 with borderline tumours, identified through a population-based cancer registry, as well as b) 1832 controls selected from the general

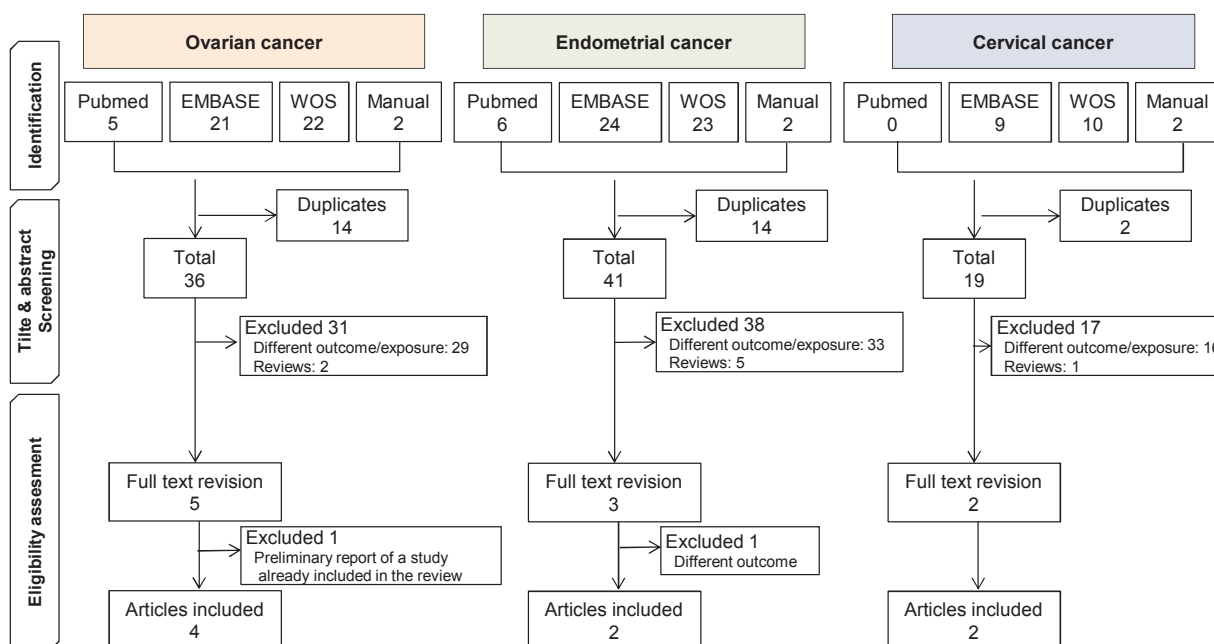


Fig. 1. Night shift work and gynaecological cancer: Search flow diagrams.

**Table 1**  
Gynecological cancer and Night Shift Work Systematic Review: Quality assessment of the studies according to Newcastle-Ottawa Scale.

Case-Control Study	Selection				Comparability			Outcome
	Cancer site (Author, year of publication)	Adequate case definition	Cases representativeness	Controls selection	Controls definition	Exposure ascertainment	Same method ascertainment for cases & controls	
	Ovary (Bhatti 2013) [21]:	☀	☀	☀	☀	☀	☀	☀
Cohort-Studies	Cancer site (Author, year of publication)	Exposed cohort representativeness	Non-exposed cohort selection	Ascertainment of exposure	Outcome not present at start	Comparability	Follow-up length (at least 15 yrs)	Follow-up adequacy (lost to follow up < 15%)
Swedish cohort	Ovary, endometrium, cervix (Schwarzbaum 2007) [24]	☀	☀		☀	☀	☀	☀
Nurses' Health study I	Ovary (Poole 2001) [23]; Endometrium (Viswanathan 2007) [25];	☀	☀	☀	☀	☀☀	☀	☀
Nurses Health Study II	Ovary (Poole 2001) [23];	☀	☀	☀	☀	☀☀	☀	☀
Cancer Prevention Study II	Ovary (Carter 2014) [22];	☀	☀	☀	☀	☀☀	☀	☀
Japan Collaborative Cohort Study for Evaluation of Cancer	Cervix (Fujino 2007) [26]:	☀		☀	☀	☀☀	☀	☀

population through random-digit-dialing (RDD), using age and county stratified sampling. To define exposure to NSW, each woman reported all the jobs held continuously for at least four months since the age of 25 and, for each one, they indicated the frequency of night work (between midnight and 4.00 am). With these data, the researchers defined diverse intensities of NSW per job (ever, less than 50% of days worked NSW and permanent NSW) and, for each participant, they calculated a life-time cumulative NSW estimator, which combined the total number of months engaged per job, the hours worked and the fraction of time spent doing nightshift per week. Those that reported having ever had NSW had a statistically increased risk of invasive ovarian cancer (OR<sub>ever</sub>:1.24;95%CI:1.04–1.49). Similar results were found in the subgroup with any job with < 50% of work days with nightshift, which could be considered rotating NSW (OR<sub>rotating</sub>:1.28; 95%CI:1.03–1.59), but the excess was not significant in those reporting any job with permanent nightshift (OR<sub>fixed</sub>:1.16; 95%CI:0.87–1.55). When examining cumulative nightshift work-years, there were no clear indications of a lineal trend, as significant increases in risk were restricted to the second highest cumulative category (> 3–7work-years). The researchers also tested a possible interaction with self-reported chronotype, which was not significant, and additional analyses showed that the risk excess for invasive tumours was restricted to women ≥ 50 years at recruitment. There were relevant differences by histological subtypes, with no association with NSW for endometroid and clear cell tumours.

In the first cohort study, Schwartzbaum et al. [24] tested this association in 1,1486,61 Swedish female workers followed during 18 years from 1971 to 1989 for the occurrence of any cancer through linkage to the Swedish Cancer Registry. The cohort comprised all Swedish women, included in the 1960 & 70 censuses, which reported working at least half-time in 1970 census. To assess NSW exposure, the researchers constructed a job-industry-exposure matrix (JEM) based on a survey about living conditions carried out in the country in random sample of 46438 persons of both sexes between 1977 and 1981. For each combination of job-industry, they calculated the proportion of employed that reported rotating work with three different time shifts or any work hour between 01:00 am-04:00 am during the week preceding the interview. If this proportion was at least 40%, the job-industry combination was classified as exposed to NSW (i.e. crane/hoist operator in basic metal industry; delivery women in paper products & printing/publishing industries; midwives); those combinations with < 30% were classified as unexposed. They did not find any association between NSW in 1970 and ovarian cancer (SIR: 0.80; 95%CI:0.45–1.32) and obtained similar results when they evaluated long-term exposure in a sub-analysis considering only those exposed to NSW in both censuses (SIR: 1.13;95%CI:0.49–2.23).

Poole et al. [23] also addressed this topic in the US, focusing specifically on rotating NSW in the NHS I & II cohorts, which included 68,999 nurses, followed during 20 years, with 524 incident ovarian cancer cases, and 112,549 younger nurses, followed-up during 18 years with 194 new cases respectively. Both cohorts shared many design characteristics but each one had specific features. The two studies identified new cases by self-reporting at biennial questionnaires and confirmed them by pathologist's review. Regarding exposure, both collected the self-reported number of years with rotating shifts with at least 3 nights per month. However, in NHS II cohort this information was updated four times during follow up. Again, researchers did not find any association between ovarian cancer risk and having ever had NSW in any of the cohorts (RR<sub>rotating\_NHSI</sub>:1.07;95%CI:0.96–1.18;RR<sub>rotating\_NHSII</sub>:0.87;95%CI:0.70–1.07) nor in their pooled analysis (RR<sub>rotating\_pool</sub>:1.28;95%CI: 0.84–1.94), nor when length of exposure was taken into account (see Table 2).

Finally, the American Cancer Society's Cancer Prevention Study II focused on NSW and fatal ovarian cancer [22]. The cohort was made-up from volunteers recruited along the USA. In this analysis, Carter et al. included 161,004 employed women with 28 years of follow-up and 1289 deaths due to ovarian cancer, identified by active search of cancer death certificates

**Table 2**  
Association of gynaecological cancer and nightshift work: summary of published studies.

Case-Control Studies		Cohort-Studies															
Author, Country (year of publication) Study name	Recruit period	Outcome assessed	Case source	Exclusion criteria	Age (yrs)	Control selection	Controls (n)	Cases (n)	Participation rate (%)	Confounders assessed	Source	Type of NSW	Night shift time (hours)	Period of exposure	OR	95%CI	
Mean Range																	
Cases Controls																	
<i>Ovarian cancer</i> Bhatti, USA (2013) [21]	2002–09	Incidence	Cancer registry	Language barrier	56 <sup>i</sup>	Random digital dialing	1832	1101	74.2	Age, parity, duration of OC, HRT, BMI at age 30 & others <sup>o</sup>	Self-reported	Any	Including 12pm–4am	Ever-never	1.24	1.04–1.49	
												Rotating <sup>b</sup>	Rotating <sup>b</sup>	Ever-never	1.28	1.03–1.59	
											Fixed	Fixed	Fixed	Ever-never	1.16	0.87–1.55	
Cohort-Studies																	
Author, Country (year of publication) Study name	Start of follow up	Outcome assessed	Base pop.	Exclusion criteria	Age <sup>c</sup> (yrs)	Case ascertainment	Cohort size (n)	Total Cases (n)	Exposed (%)	Follow-up	Confounders assessed	Source	Type of NSW	Night shift time (hours)	Period of exposure	RR	95% CI
Mean Range																	
Years Lost (%)																	
<i>Ovarian cancer</i> Schwartzbaum, Sweden (2007) [24]	1971	Incidence	Working Pop.	n/a	39 <sup>i</sup>	Cancer Registry	1148661	n/a	0.3	18	Age & others <sup>d</sup>	JEM	NSW in 1970		Ever-never	0.80	0.45–1.32
									n/a	n/a			NSW in 1960 & 1970		≥ 10 yrs	1.13	0.49–2.23
Poole, USA (2011) Nurses' Health study I [23]	1988	Incidence	Occup (nurses)	Women with bilateral oophorectomy, menopause due to pelvic irradiation, missing basic information	54	Self reported + clinical confirmed	68999	524	59	20	Age, family history of ovarian cancer, menopausal status, parity, OC, HRT, BMI, breastfeeding, smoking, tubal ligation & others <sup>e</sup>	Self-reported	Rotating nightshifts (at least three times per month)	1–2 yrs 3–5 yrs 6–9 yrs 10–14 yrs 15–19 yrs 20+ yrs	Ever-never	1.07	0.94–1.21
Poole, USA (2011) Nurses' Health study II [23]	1989	Incidence	Occup (nurses)	Women with bilateral oophorectomy, menopause due to pelvic irradiation, missing basic information	35	Self reported + clinical confirmed	112549	194	67.8	20	Age, family history of ovarian cancer, menopausal status, parity, OC, HRT, BMI, breastfeeding, smoking, tubal ligation & others <sup>e</sup>	Self-reported (four updates)	Rotating nightshifts (at least three times per month)	1–2 yrs 3–5 yrs 6–9 yrs 10–14 yrs 15–19 yrs	Ever-never	0.88	0.56–1.37
										12.4	Age, family history of ovarian cancer, menopausal status, parity, OC, HRT, BMI, breastfeeding, smoking, tubal ligation & others <sup>e</sup>	Self-reported (four updates)	Rotating nightshifts (at least three times per month)	1–2 yrs 3–5 yrs 6–9 yrs 10–14 yrs 15–19 yrs	Ever-never	0.87	0.72–1.05
											Age, family history of ovarian cancer, menopausal status, parity, OC, HRT, BMI, breastfeeding, smoking, tubal ligation & others <sup>e</sup>	Self-reported (four updates)	Rotating nightshifts (at least three times per month)	1–2 yrs 3–5 yrs 6–9 yrs 10–14 yrs 15–19 yrs	Ever-never	0.80	0.56–1.14
											Age, family history of ovarian cancer, menopausal status, parity, OC, HRT, BMI, breastfeeding, smoking, tubal ligation & others <sup>e</sup>	Self-reported (four updates)	Rotating nightshifts (at least three times per month)	1–2 yrs 3–5 yrs 6–9 yrs 10–14 yrs 15–19 yrs	Ever-never	0.79	0.52–1.18
											Age, family history of ovarian cancer, menopausal status, parity, OC, HRT, BMI, breastfeeding, smoking, tubal ligation & others <sup>e</sup>	Self-reported (four updates)	Rotating nightshifts (at least three times per month)	1–2 yrs 3–5 yrs 6–9 yrs 10–14 yrs 15–19 yrs	Ever-never	0.80	0.47–1.35
											Age, family history of ovarian cancer, menopausal status, parity, OC, HRT, BMI, breastfeeding, smoking, tubal ligation & others <sup>e</sup>	Self-reported (four updates)	Rotating nightshifts (at least three times per month)	1–2 yrs 3–5 yrs 6–9 yrs 10–14 yrs 15–19 yrs	Ever-never	1.25	0.70–2.24
											Age, family history of ovarian cancer, menopausal status, parity, OC, HRT, BMI, breastfeeding, smoking, tubal ligation & others <sup>e</sup>	Self-reported (four updates)	Rotating nightshifts (at least three times per month)	1–2 yrs 3–5 yrs 6–9 yrs 10–14 yrs 15–19 yrs	Ever-never	1.21	0.48–3.02

(continued on next page)

Table 2 (continued)

Cohort-Studies	Author, Country (Year of publication) Study name	Start of follow up	Outcome assessed	Base pop.	Exclusion criteria	Age <sup>c</sup> (yrs)		Case ascertainment	Cohort size (n)	Total Cases (n)	Exposed (%)	Follow-up		Source	Type of NSW	Night shift time (hours)	Period of exposure	RR	95% CI
						Mean	Range					Years	Lost (%)						
						50	n/a					28	n/a						
	Carter, USA (2014) American Prevention Study II [22]	1982	Mortality	Volunteer	Prevalent cancer, ovarian surgery, hysterectomy, artificially induced menopause, missing basic information, not employed	50	n/a	National Death Index	161004	1289	6.6	28	n/a	Self-reported	Rotating shifts (not necessarily including night)	Start 9–12pm	Ever-never	1.27	1.03–1.56
	<i>Endometrial cancer</i> Viswanathan, USA (2007) Nurses' Health Study I [25]	1988	Incidence	Occup (Nurses)	Any previous cancer hysterectomy	54	42–67	Self reported + clinical confirmed	53487	515	58.7	16	< 10%	Self-reported	Rotating nightshifts	Ever-never	1.01	0.87–1.17	
	Schwartzbaum, Sweden (2007) [24]	1971	Incidence	Working Pop	n/a	39	16–67	Cancer Registry	1148661	n/a	n/a	18	n/a	JEM	NSW in 1970	Ever yrs	1.01	0.59–1.62	
	<i>Cervical cancer</i> Schwartzbaum, Sweden (2007) [24]	1971	Incidence	Working Pop	n/a	39	16–67	Cancer Registry	1148661	n/a	0.3	18	n/a	JEM	NSW in 1970	Ever-never	1.39	0.82–2.19	
	Fujino (2007) JACC [26]	1988–90	Mortality	Mixed	n/a	58 <sup>i</sup>	40–79	Cancer Registry	64327	21	n/a	n/a	3.1	Self-reported	Rotating nightshifts	n/a	2.05	0.60–7.06	

Yrs (years), NSW (nightshift work), OR (odds ratio), CI (confidence interval), Pop (Population), Occup (Occupational), OC (oral contraception), HRT (hormone replacement therapy), BMI (body mass index), JEM (job exposure matrix); n/a (not available).

<sup>a</sup> Country of residence, year of diagnosis, race, smoking, alcohol, & education.  
<sup>b</sup> NSW < 50% working days.  
<sup>c</sup> At start of follow up.  
<sup>d</sup> Occup position, county of residence, marital status, urbanization, socioeconomic status.  
<sup>e</sup> Menstrual regularity, infertility.  
<sup>f</sup> Height, insomnia, sleep duration, family history of breast ca, age at first birth, use of sleeping pills, race, alcohol use, education.  
<sup>g</sup> Height, smoking, aspirin, alcohol & h-blocker use, diabetes, hypertension, total energy intake, intrauterine device, physical activity, waist-hip ratio, socioeconomic status, race, BMI at age 18, geographic region.  
<sup>h</sup> Study area.  
<sup>i</sup> Estimation based on age categories.

and national death index. Participants were classified in excluding categories based on information provided at recruitment as a) declaring any rotating shifts – without any specific mention to inclusion of nightshift; b) fixed night workers: not rotating and initial working time between 9:00 pm and 0:00 am; and c) fixed day workers. Compared to fixed daytime work, rotating-shift work was associated with an elevated risk of lethal ovarian cancer ( $RR_{\text{rotating}}:1.27;95\%CI:1.03-1.56$ ). This association was not found for fixed NSW ( $RR_{\text{fixed}}:1.12;95\%CI:0.67-1.87$ ).

### 3.3. Endometrial cancer

Two of the previously described studies – Swedish cohort and Nurse Health Study I- provided also risk estimates for NSW and endometrial cancer. In the Swedish report by Schwartzbaum et al. [24], NSW was not associated to this tumour, either in those exposed in 1970 (SIR: 1.01; 95%CI:0.59–1.62), nor in the subset of long-term exposure (SIR: 1.13; 95%CI:0.49–2.22). In contrast, the analysis of NHS I of Viswanathan et al. [25], which included 53,487 nurses followed during 16 years, with 515 incident endometrial tumours, found an increased risk in long-term rotating NSW ( $RR_{\text{rotating} > 20\text{yrs}}:1.47;95\%CI:1.03-2.10$ ;  $p_{\text{trend}} < 0.05$ ) and a significant trend with years of exposure. Both associations were only observed in those nurses with BMI  $\geq 30$  ( $RR_{\text{rotating} > 20\text{yrs}}:2.09;95\%CI:1.24-3.52$ ;  $p_{\text{trend}} < 0.001$ ) when this interaction was taken into account.

### 3.4. Cervical cancer

In the Swedish cohort [24], Schwartzbaum et al. found a similar non-significant increase of risk for cervix carcinoma with NSW in 1970 (SIR:1.39;95%CI:0.82–2.19) and in those with long-term NSW (SIR:1.43;95%CI:0.46–3.34). The other study with risk estimates for NSW and cervical cancer – in this case, mortality – was the Japan Collaborative Cohort Study (JACC). However, the report made by Fujino et al. [26] does not provide information on the total number of women or about follow-up time included in the analysis. According to other JACC publication [29] participants reported their life-time predominant work schedule before recruitment (fixed daytime, fixed night time or rotating shift work including night). Of the 21 deaths due to cervical cancer, 3 corresponded to women with rotating nightshifts ( $HR_{\text{rotating}}:2.05;95\%CI:0.60-7.06$ ), and none to those with permanent night-work.

## 4. Discussion

This review aimed to synthesize the available information on the possible association between NSW and gynaecological tumours. Our results show that this issue has been given scarce attention, and that the little evidence available does not show any clear pattern of association between ovarian, endometrial or cervical cancer incidence and this occupational risk factor. We did not find any study that evaluated its relationship with vulvar and vaginal tumours.

Globally, the results of the studies found in our search were contradictory or null. Of the four articles exploring the NSW with ovarian cancer, two studies did not detect any relationship, another found higher risk among those ever exposed and, in the last one, the association was only significant in rotating shift workers. Regarding endometrial cancer, while one study did not detect any association, the other found an increased risk among nurses with long-term exposure. For cervical cancer, none of the two reviewed studies detected a significant increased risk. Design differences might account for the heterogeneity in these results, as well as differences in exposure definition (self-reported or using a job exposure matrix), in the NSW pattern (rotating, fixed or any), in the period of exposure (ever/never vs long-term), and in the control of potential confounders.

These limited data are insufficient to evaluate the relationship between NSW and these tumours. Nevertheless, none of them would be

implausible from a biological point of view. Work in night shifts produces circadian disruption, resulting in widespread deregulation of clock-controlled biological processes and melatonin suppression [4]. Melatonin inhibits estrogen receptors and can counteract the tumour-promoting effects of estrogens [4]. In vitro and in vivo studies also suggest that membrane and intracellular actions of melatonin lead to inhibition of cell proliferation, survival, migration, inflammation, and angiogenesis of ovarian [30], and also probably endometrial [31] cancers. In addition, aberrant expression of circadian clock genes has been found in ovarian and endometrial cancers [32]; disruption of the circadian system also affects metabolic processes and predisposes the organism to adiposity [4], which is strongly associated with both cancer sites [33]. Regarding cervical cancer, recent research highlights the synergic role of estrogens and the human papilloma virus [34], and long-term use of antiestrogen therapy seems to confer lower risk of cervical neoplasia to women with a previous breast tumour [35].

One of the relevant and well-known problems in the study of NSW is the difficulty of having a good assessment of exposure [36], because different patterns might have different biological effects. Interestingly, most of the statistically significant results observed are associated with rotating nightshifts. Thus, Bhatti et al. [21] and Carter et al. [22] showed that rotating-shift work was associated with an elevated risk of invasive [21] or fatal [22] ovarian cancer. Viswanathan et al. [25] also found an increased risk of endometrial cancer in nurses with many years of rotating NSW. Previous studies suggest that the intensity and frequency of NSW determine its capacity for disruption [36], and it is possible that women who perform fixed night shifts may modify their biological clock to get used to them. Data in Table 2 also show higher risk estimates for long-term exposures, which would be in line with the results reported for breast cancer [37] and for mammographic density [38]. Another issue that remains almost unexplored is whether there are differences by histological subtype, age or chronotype – only studied for ovarian cancer by Bhatti et al. [21], and the possible role of other factors such as BMI as effect modulators as suggested by Viswanathan et al. [25] for endometrial tumours.

Even though the low number of data per site made us decide not to calculate pool risk estimates, we consider that one of the strengths of this review is the evaluation of the quality of the studies. The Newcastle-Ottawa scale is relatively easy to use and it has been judged to be suitable for systematic reviews [39]. However, NOS has also some limitations. For example, it does not take into account the appropriateness of the analysis or the sample size; in addition, for the comparability domain, it does not include baseline comparability assessment and the selection of the risk factors is subjective.

In this case, NOS evaluation points out that most of our cohorts do not represent general population, with nurses being the most studied subgroup. As we have mentioned, it is also difficult to have a good exposure assessment. Recall bias is very unlikely in prospective studies, but misclassification is probably present in all the selected studies. In most of them, researchers have used self-reported information on present or/and past NSW collected just at recruitment, and only NHS II updated these data during the follow-up. Bhatti et al. [21] obtained lifetime history of NSW job by job, although they failed to assess intensity of nightshifts schedules, Poole et al. [23] did not collect data on permanent or infrequent rotating NSW and Schwartzbaum et al. [24] assessed exposure on aggregated categories. Finally, although uncontrolled confounding can be present in all studies, it is a more obvious problem in Schwartzbaum et al. [24], Fujino et al. [26] and Bhatti et al. [21].

In summary, the few available epidemiological studies and the heterogeneity of the observed results make us conclude that there is not enough evidence to evaluate whether there is any relationship between NSW and gynaecological tumours. Further rigorous prospective studies with detailed and well-defined exposure information, with a wider range of occupational groups, with better control for potential confounders and with more data on proposed biological mechanisms are

needed to fill this gap of knowledge.

## Contributors

Christine Schwarz, Ana María Pedraza-Flechas and Beatriz Perez-Gomez conceived the idea, performed the search and drafted the manuscript.

Virginia Lope, Roberto Pastor-Barriuso and Marina Pollan collaborated in the analysis.

All authors made substantial contributions to the discussion and participated in the elaboration of the definitive version of the paper.

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## Conflict of interest

The authors declare that they have no conflict of interest.

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