Human Breast Cancer

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Draft RoC Monograph on Night Shift Work and Light at Night
Peer Review Meeting
5 October 2018

Outline

| Background	• Overview of breast cancer • Overview of methods
Night shift work	• Utility of breast cancer studies • Assessment of findings • Preliminary level of evidence conclusions
Light at night	• Assessment of findings • Preliminary level of evidence conclusions
Transmeridian travel	• Assessment of findings • Preliminary level of evidence conclusions

Female Breast Cancer - Background

Breast cancer incidence, trends, mortality and survival

- Incidence is high (126/100,000/yr) and rising (0.3%/yr for last 10 yrs)*

- Mortality is low (20.9/100,000/yr) and 5-year survival high (89.7%)*
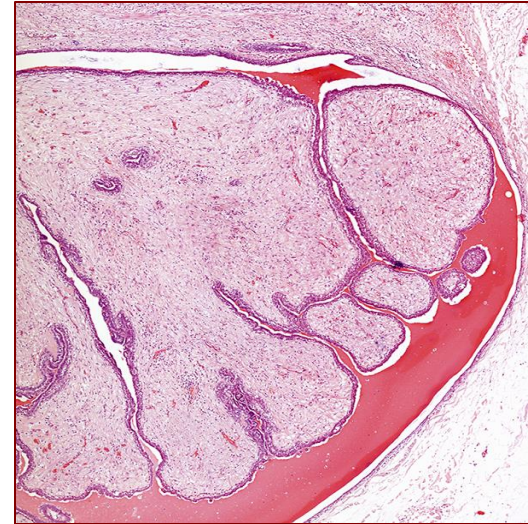
Breast cancer subtypes and etiology

- ~2 out of 3 breast cancers are ER+ or PR+ (estrogen or progesterone positive). For hormone positive tumor subtypes, high estrogen levels promote cancer growth and spread

- Breast tissue more susceptible before first full-term pregnancy or at younger ages when breast cells are dividing
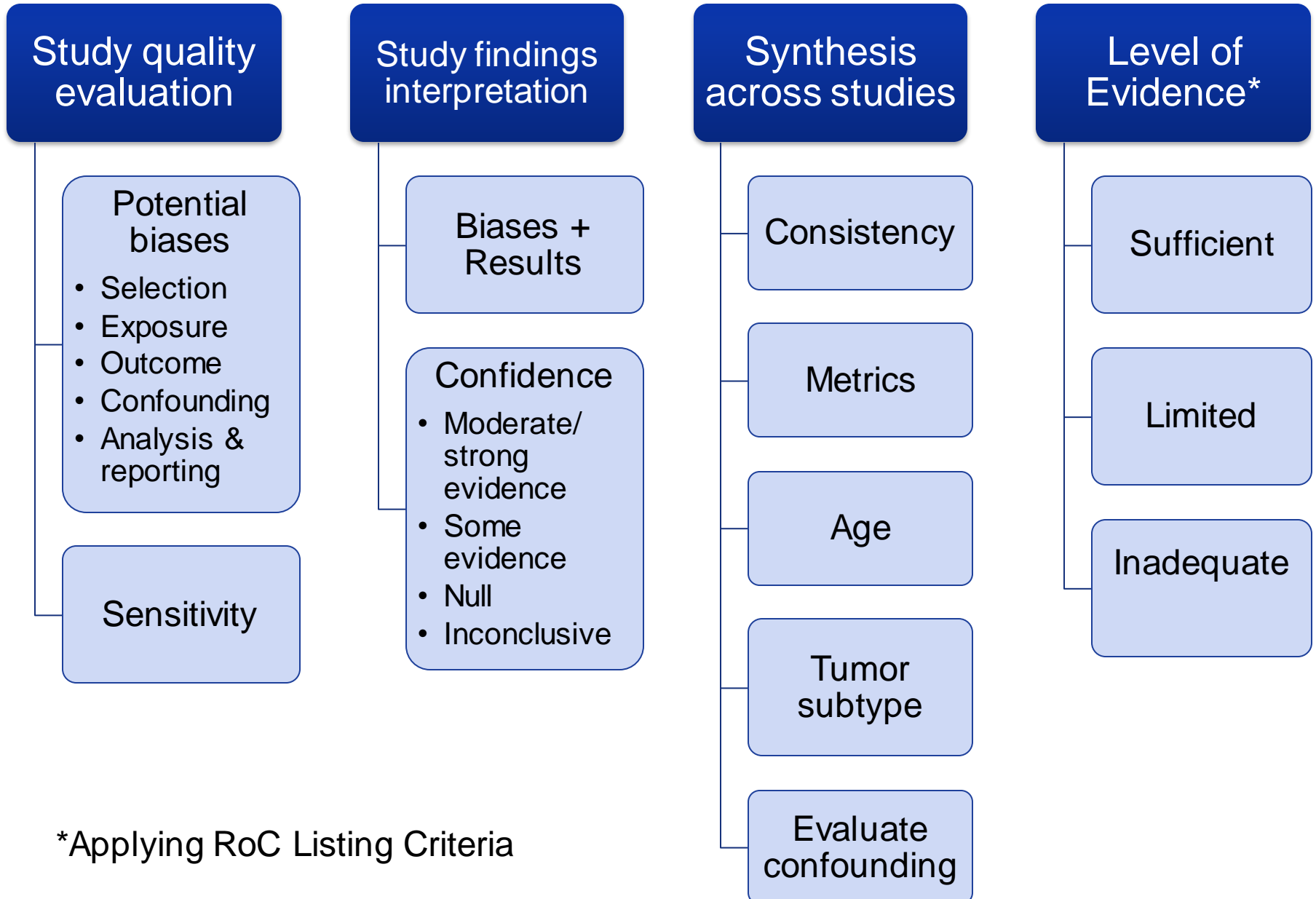
*http://seer.cancer.gov/statfacts/html/lungb.html 2011-2015

RoC Systematic Review Methods

Study quality evaluation

Potential biases
- Selection
- Exposure
- Outcome
- Confounding
- Analysis & reporting

Sensitivity

Study findings interpretation

Biases + Results

Confidence
- Moderate/ strong evidence
- Some evidence
- Null
- Inconclusive

Synthesis across studies

- Consistency
- Metrics
- Age
- Tumor subtype
- Evaluate confounding

Level of Evidence*

- Sufficient
- Limited
- Inadequate

*Applying RoC Listing Criteria

RoC Systematic Review Methods

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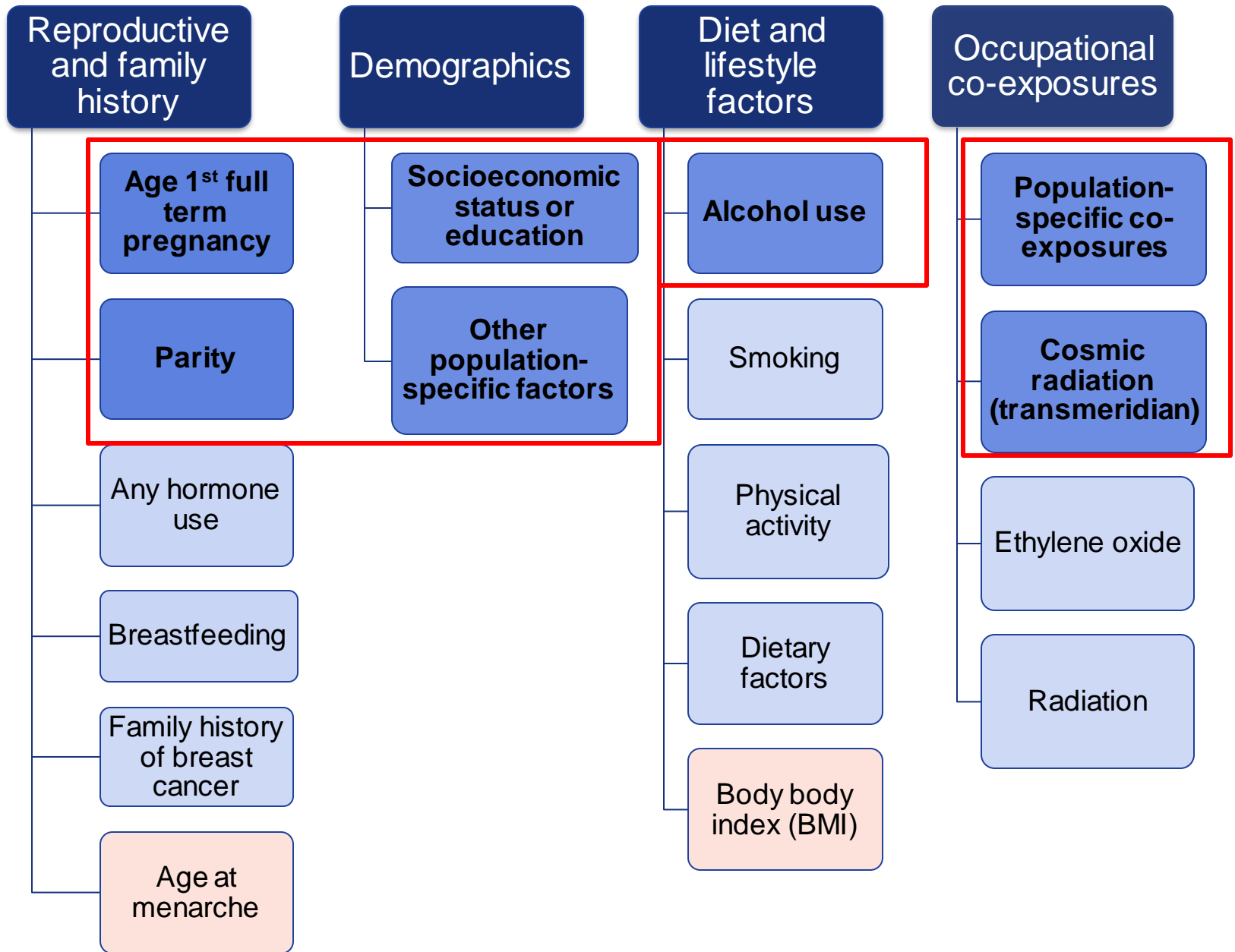**Level of Evidence***

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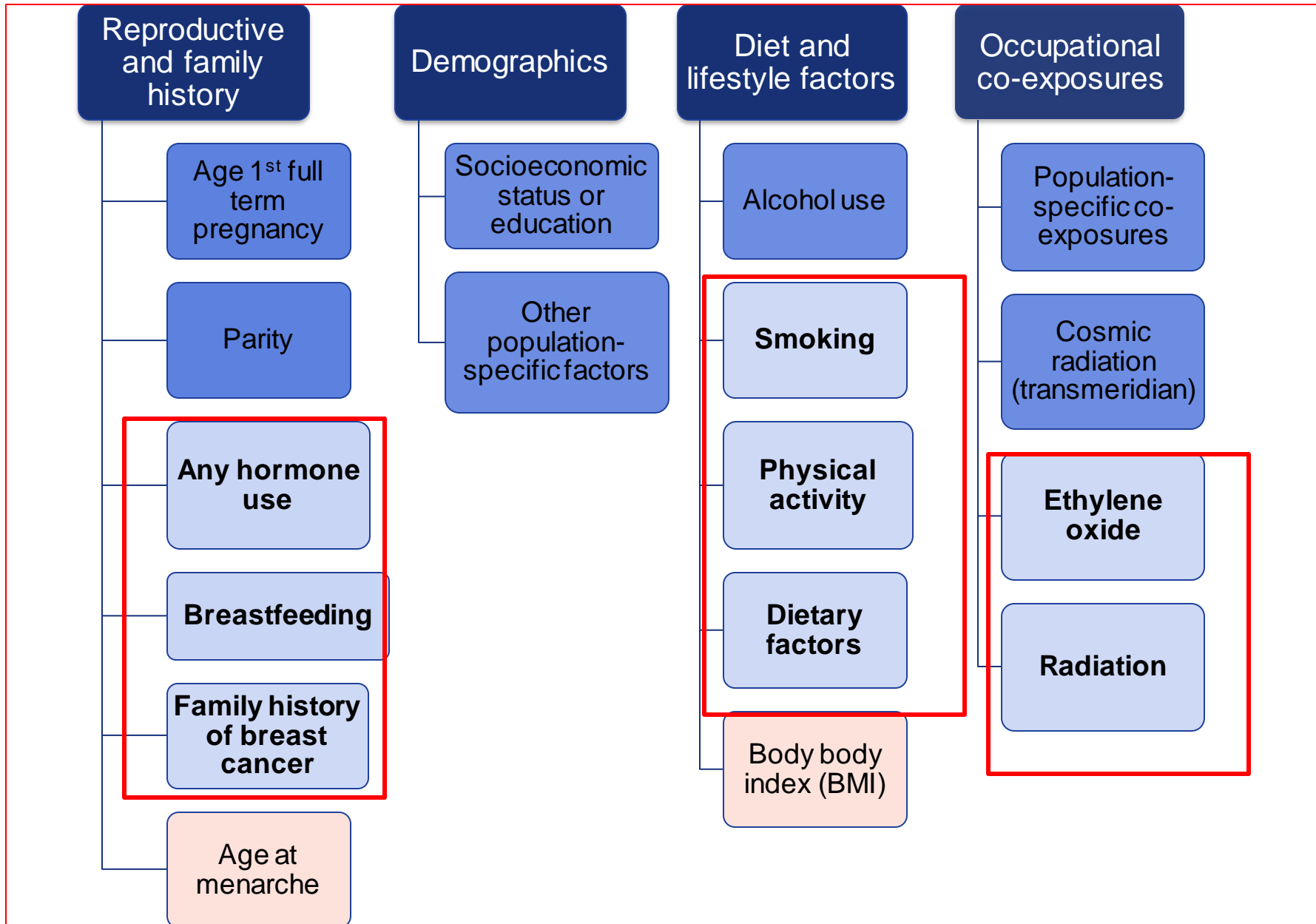
Key issues and challenges

- No direct measure of circadian disruption included
  - We looked at metrics of long duration, high frequency, and age of the populations as potential measures of circadian disruption

- Variety of exposure definitions of night work
  - e.g., 3 nights/month, 1 night/week, "usually", etc.
  - e.g., 3 hours between midnight and 6pm, 11pm to 7am; evenings and/or nights, etc.

- Older cohorts and left truncation bias

- Several potential effect modifiers
  - Chronotype
  - Menopausal status
  - Age began shift work; age since shift work ended

- Breast cancer subtypes

- No meta-analysis

Potential confounders: Key

Reproductive and family history
- **Age 1st full term pregnancy**
- **Parity**
- Any hormone use
- Breastfeeding
- Family history of breast cancer
- Age at menarche

Demographics
- **Socioeconomic status or education**
- **Other population-specific factors**

Diet and lifestyle factors
- **Alcohol use**
- Smoking
- Physical activity
- Dietary factors
- Body body index (BMI)

Occupational co-exposures
- **Population-specific co-exposures**
- **Cosmic radiation (transmeridian)**
- Ethylene oxide
- Radiation

Potential confounders: Weak or population specific

Reproductive and family history
- Age 1st full term pregnancy
- Parity
- **Any hormone use**
- **Breastfeeding**
- **Family history of breast cancer**
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Potential confounders: Causal Pathway

Reproductive and family history
- Age 1st full term pregnancy
- Parity
- Any hormone use
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Demographics
- Socioeconomic status or education
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Diet and lifestyle factors
- Alcohol use
- Smoking
- Physical activity
- Dietary factors
- **Body body index (BMI)**

Occupational co-exposures
- Population-specific co-exposures
- Cosmic radiation (transmeridian)
- Ethylene oxide
- Radiation

Utility of Cohort Studies of Night Shift Work

Author, Date	Utility rationale	Utility
Wegrzyn 2017, U.S.	• Good exposure assessment • Multiple metrics • Moderate or high sensitivity • Minimal chance of selection or confounding bias	High +++
Knutsson 2013, Sweden Li 2015, Shanghai Vistisen 2017, Denmark	• Moderate exposure assessment • Varying sensitivity (high to low) • Low risk of other bias	Moderate ++
Åkerstedt 2015, Sweden Pronk 2010, Shanghai Travis 2016, Million Women, U.K. Travis 2016, EPIC Oxford, U.K. Tynes 1996, Norway	• Low exposure assessment • Potential selection bias • Low sensitivity	Low +
Jorgensen 2017, Denmark Koppes 2014, Netherlands Schwartzbaum 2007, Sweden Travis 2016, U.K.	• Mortality study • Only current exposure to night work • Credibility of night work rates in question	Inadequate 0

Utility of Case-Control Studies of Night Shift Work

Population, Author, Date	Utility Rationale	Utility
Fritschi 2013, Western Australia Hansen & Lassen 2012, Denmark Hansen & Stevens 2012, Denmark Menegaux 2013, France Papantoniou 2015, Spain	• Good exposure assessment • Multiple metrics • Moderate or high sensitivity • Minimal chance of selection or confounding bias	High +++
Grundy 2013, Canada Lie 2011, Norway Pesch 2010, Germany Davis 2001, Seattle, WA	• Moderate exposure assessment • Varying sensitivity (high to low) • Low risk of other bias	Moderate ++
Wang 2015, Guangzhou, China O'Leary 2006, Long Island NY Hansen 2001, Denmark	• Low exposure assessment • Potential selection bias • Low sensitivity	Low +

Study quality evaluation

Potential biases
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- Exposure
- Outcome
- Confounding
- Analysis & reporting

Sensitivity

Study findings interpretation

Biases + Results

Confidence
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Synthesis across studies

Consistency

Metrics

Age

Tumor subtype

Evaluate confounding
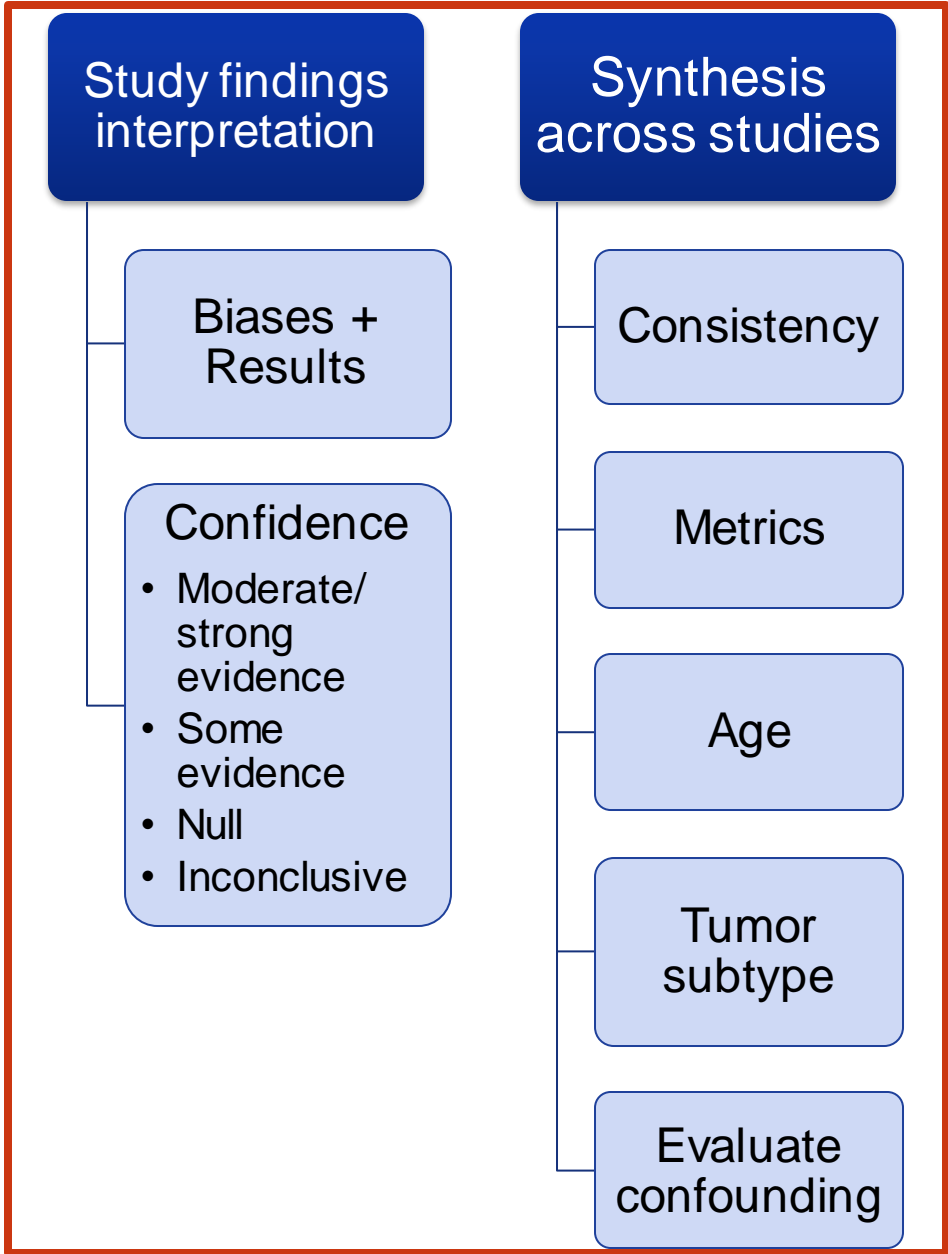
Level of Evidence*

Sufficient

Limited

Inadequate

*Applying RoC Listing Criteria

Confidence in each study's findings

Moderate to strong evidence	• RR ≥ 1 for several exposure metrics or effect modification • Most RRs are statistically significant or have a positive exposure response relationship • Moderate to high quality studies
Some evidence	• Significant RR ≥ 1 for at least one exposure metric or weaker patterns of effect for several metrics • Moderate or high quality studies; low quality studies with bias towards the null
Null	• RR ≤ 1.0 • Study quality vary
Inconclusive	• RRs vary • Unknown direction of bias or potential confounding • Low precision

RR = relative risk

Reference	Utility	Ever NSW	Years	Frequent	Young age
Wegrzyn 2017	Hi+Mod		+++		+++
Davis 2001	Hi+Mod	++	+++	+++	
Grundy 2013	Hi+Mod		+	+++	I
Hansen and Lassen 2012	Hi+Mod	+	+++	+++	
Hansen and Stevens 2012	Hi+Mod	+++	+++	+++	
Lie 2011, Lie 2013	Hi+Mod			+++	
Menegaux 2013	Hi+Mod	++	+	++	+++
Knutsson 2013	Hi+Mod	+++			+
Fritschi 2013	Hi+Mod	++	+		+
Papantoniou 2015	Hi+Mod	+	+	+	++
Pesch 2010	Hi+Mod	Null	+	+	++
Åkerstedt 2015	Low	Null	++		+
Travis, UK EPIC Oxford 2016	Low	Null	++		
Travis, Million Women Study 2016	Low	Null	++		
Tynes 1996	Low		+++		++
Hansen 2001	Low	++	++		–
Wang 2015	Low	++			+
Li 2015	Hi+Mod		Null	Null	Null
Vistisen 2017	Hi+Mod	Null			
Pronk 2010	Low	Null	Null	Null	Null
O'Leary 2006	Low	-			

Moderate to strong evidence

Some evidence

Null

Classification of the evidence allows a comprehensive picture of the study and consideration of the potential for bias

Hi+Mod = informative (dark yellow); Low = low utility (light yellow); strength of association increases with number of + and darker shade of blue

Breast Cancer and Night Shift Work

Excess risk of breast cancer with ever night shift work in high and moderate utility studies
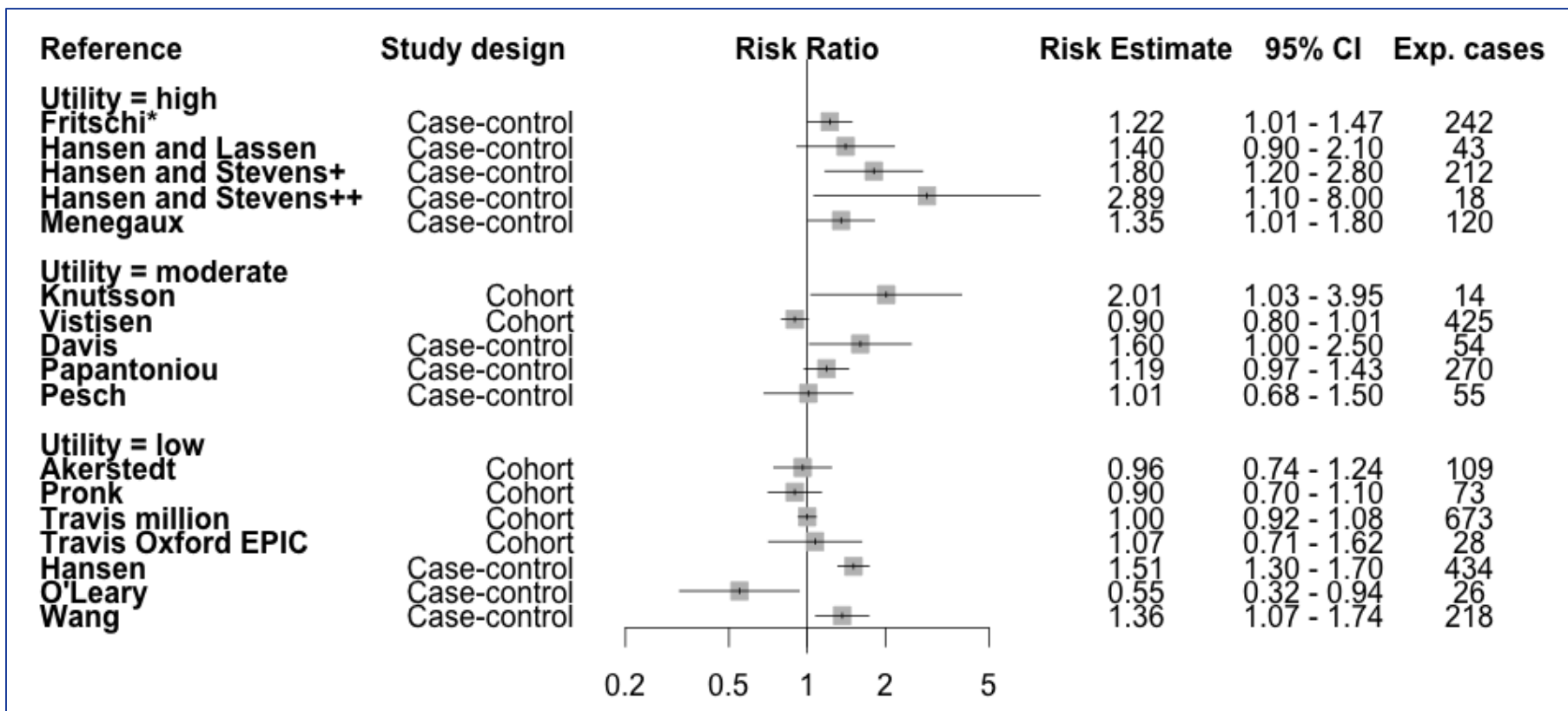
Plotted points are based on calculated estimates (R statistical package) and may differ slightly from published estimates.
*Trend $P = 0.04$ for phase shift.
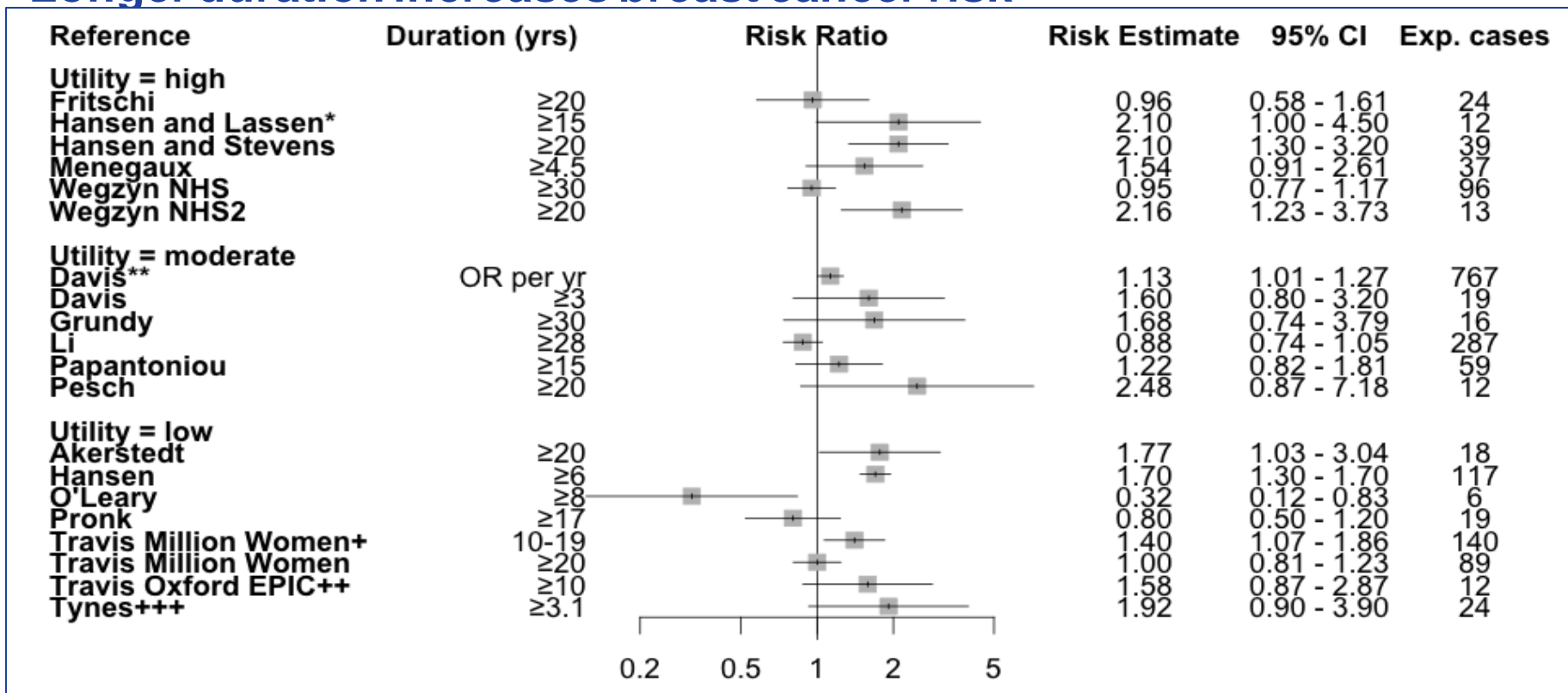+Rotating night shift without permanent nightwork.
++Rotating night shifts with permanent nightwork.

Breast Cancer and Night Shift Work

Longer duration increases breast cancer risk

Reference	Duration (yrs)	Risk Ratio	Risk Estimate	95% CI	Exp. cases
Utility = high					
Fritschi	≥20		0.96	0.58 - 1.61	24
Hansen and Lassen*	≥15		2.10	1.00 - 4.50	12
Hansen and Stevens	≥20		2.10	1.30 - 3.20	39
Menegaux	≥4.5		1.54	0.91 - 2.61	37
Wegzyn NHS	≥30		0.95	0.77 - 1.17	96
Wegzyn NHS2	≥20		2.16	1.23 - 3.73	13
Utility = moderate					
Davis**	OR per yr		1.13	1.01 - 1.27	767
Davis	≥3		1.60	0.80 - 3.20	19
Grundy	≥30		1.68	0.74 - 3.79	16
Li	≥28		0.88	0.74 - 1.05	287
Papantoniou	≥15		1.22	0.82 - 1.81	59
Pesch	≥20		2.48	0.87 - 7.18	12
Utility = low					
Akerstedt	≥20		1.77	1.03 - 3.04	18
Hansen	≥6		1.70	1.30 - 1.70	117
O'Leary	≥8		0.32	0.12 - 0.83	6
Pronk	≥17		0.80	0.50 - 1.20	19
Travis Million Women+	10-19		1.40	1.07 - 1.86	140
Travis Million Women	≥20		1.00	0.81 - 1.23	89
Travis Oxford EPIC++	≥10		1.58	0.87 - 2.87	12
Tynes+++	≥3.1		1.92	0.90 - 3.90	24

Risk Ratio axis: 0.2 0.5 1 2 5

Plotted points are based on calculated estimates (R statistical package) and may differ slightly from published estimates

*Trend is $P = 0.03$.

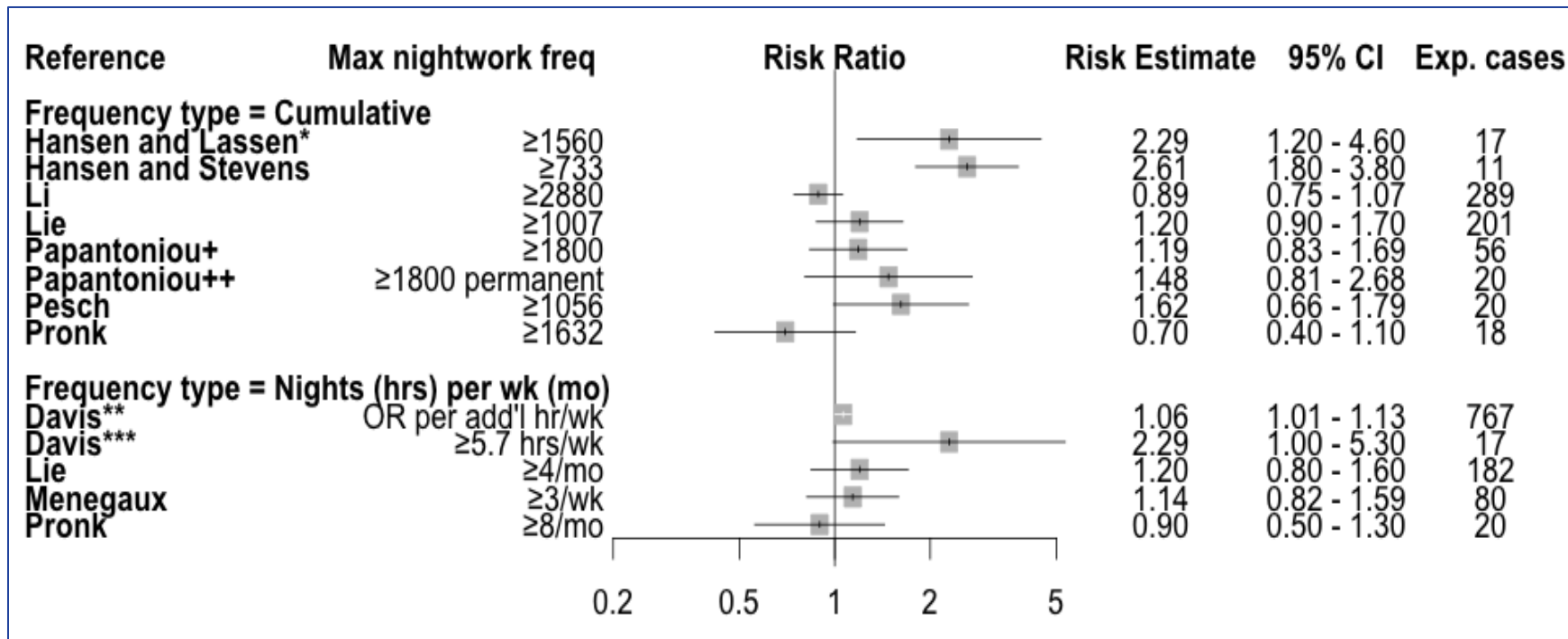** Trend is $P = 0.04$ for continuous duration.

+Travis Million Women study OR = total years worked among women last working nights in past 10 years ++Travis Oxford EPIC study OR = combined categories of 10-19 and 20+ yrs by a fixed-effects model (NTP)

+++ Combined estimate for duration for all women in the Tynes et al. study was calculated using reported frequencies for women < 50 and ≥ 50 years of age (NTP)

Higher night work frequency increases risk of breast

Reference	Max nightwork freq	Risk Ratio	Risk Estimate	95% CI	Exp. cases
Frequency type = Cumulative					
Hansen and Lassen*	≥1560		2.29	1.20 - 4.60	17
Hansen and Stevens	≥733		2.61	1.80 - 3.80	11
Li	≥2880		0.89	0.75 - 1.07	289
Lie	≥1007		1.20	0.90 - 1.70	201
Papantoniou+	≥1800		1.19	0.83 - 1.69	56
Papantoniou++	≥1800 permanent		1.48	0.81 - 2.68	20
Pesch	≥1056		1.62	0.66 - 1.79	20
Pronk	≥1632		0.70	0.40 - 1.10	18
Frequency type = Nights (hrs) per wk (mo)					
Davis**	OR per add'l hr/wk		1.06	1.01 - 1.13	767
Davis***	≥5.7 hrs/wk		2.29	1.00 - 5.30	17
Lie	≥4/mo		1.20	0.80 - 1.60	182
Menegaux	≥3/wk		1.14	0.82 - 1.59	80
Pronk	≥8/mo		0.90	0.50 - 1.30	20

0.2   0.5   1   2   5

Plotted points are based on calculated estimates (R statistical package) and may differ slightly from published estimates
*Trend is $P = 0.02$.
**Trend is $P = 0.03$.
***Trend is $P = 0.04$.
+Refers to cumulative number of all night shifts.
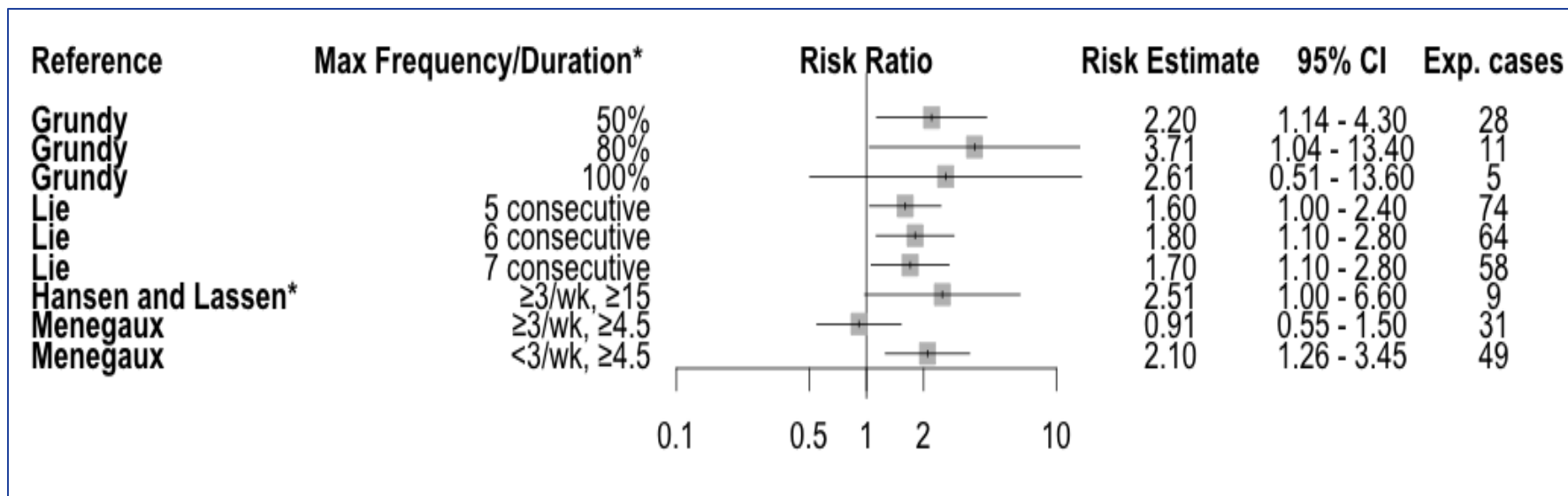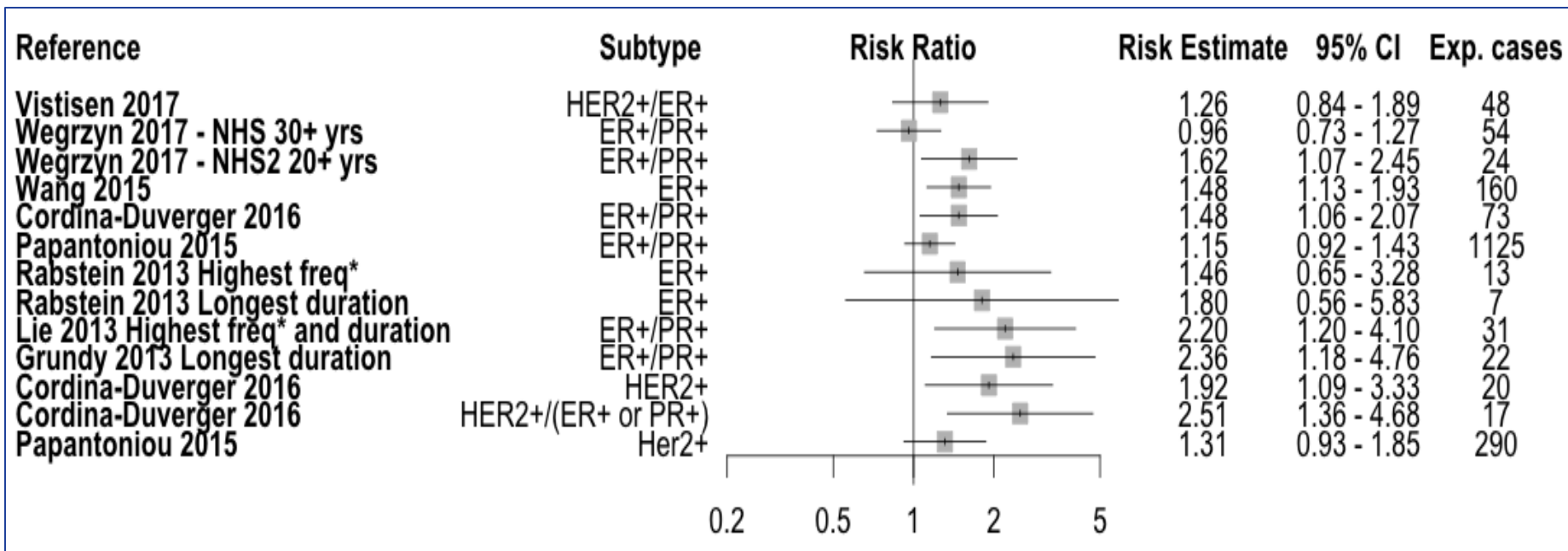++Refers to cumulative number of permanent night shifts only.
Pronk et al. only low utility study

Persistent exposures increase breast cancer risk*

Reference	Max Frequency/Duration*	Risk Ratio	Risk Estimate	95% CI	Exp. cases
Grundy	50%		2.20	1.14 - 4.30	28
Grundy	80%		3.71	1.04 - 13.40	11
Grundy	100%		2.61	0.51 - 13.60	5
Lie	5 consecutive		1.60	1.00 - 2.40	74
Lie	6 consecutive		1.80	1.10 - 2.80	64
Lie	7 consecutive		1.70	1.10 - 2.80	58
Hansen and Lassen*	≥3/wk, ≥15		2.51	1.00 - 6.60	9
Menegaux	≥3/wk, ≥4.5		0.91	0.55 - 1.50	31
Menegaux	<3/wk, ≥4.5		2.10	1.26 - 3.45	49

Risk Ratio axis: 0.1 0.5 1 2 10

Plotted points are based on calculated estimates (R statistical package) and may differ slightly from published estimates

*Highest frequency and longest duration in high and moderate utility studies

Breast Cancer and Night Shift Work

Night shift work is related to receptor positive and HER2 neu+ breast cancer*

Reference	Subtype	Risk Ratio	Risk Estimate	95% CI	Exp. cases
Vistisen 2017	HER2+/ER+		1.26	0.84 - 1.89	48
Wegrzyn 2017 - NHS 30+ yrs	ER+/PR+		0.96	0.73 - 1.27	54
Wegrzyn 2017 - NHS2 20+ yrs	ER+/PR+		1.62	1.07 - 2.45	24
Wang 2015	ER+		1.48	1.13 - 1.93	160
Cordina-Duverger 2016	ER+/PR+		1.48	1.06 - 2.07	73
Papantoniou 2015	ER+/PR+		1.15	0.92 - 1.43	1125
Rabstein 2013 Highest freq*	ER+		1.46	0.65 - 3.28	13
Rabstein 2013 Longest duration	ER+		1.80	0.56 - 5.83	7
Lie 2013 Highest freq* and duration	ER+/PR+		2.20	1.20 - 4.10	31
Grundy 2013 Longest duration	ER+/PR+		2.36	1.18 - 4.76	22
Cordina-Duverger 2016	HER2+		1.92	1.09 - 3.33	20
Cordina-Duverger 2016	HER2+/(ER+ or PR+)		2.51	1.36 - 4.68	17
Papantoniou 2015	Her2+		1.31	0.93 - 1.85	290

* Freq = frequency
Only high and moderate utility studies

Breast Cancer and Night Shift Work

Long duration, high frequency at younger ages increases risk of breast cancer

Exposure group	HR (95% CI)	Exposure group	OR (95% CI)
NHS and NHS2 cohorts Wegrzyn *et al.* 2017		**Pooled analysis of 5 studies+** Cordina-Duverger *et al.* 2018	
NHS2 (younger)		Pre-menopausal	
Duration (yr)* & follow up (FU)		≥ 3 nights/wk &	
		≥ 10 yrs	2.55 (1.03 – 6.30)
≥ 20 (all)	2.15 (1.23 - 3.73)	≥ 10 hr shift	2.15 (1.21 – 3.84)
≥ 20 and ≤10 FU	2.35 (1.04-5.31)	≤ 2 yrs**	2.21 (1.30 – 3.76)
NHS (older)		Post-menopausal	
Duration (yr)* & follow up (FU)		≥ 3 nights/wk &	
		≥ 10 yrs	1.00 (0.56–1.77)
≥ 30 (all)	0.95 (0.77 - 1.17)	≥ 10 hr shift	0.90 (0.55–1.48)
≥ 30 and ≤10 FU	1.26 (0.97 - 1.64)	≤ 2 yrs**	1.58 (0.68–3.64)

*Since baseline,

** Since last exposure

+Includes studies by Pesch et al. 2010, Fritschi et al. 2013, Grundy et al. 2013, Menegaux et al. 2013, Papantoniou et al. 2015.

RoC Systematic Review Methods
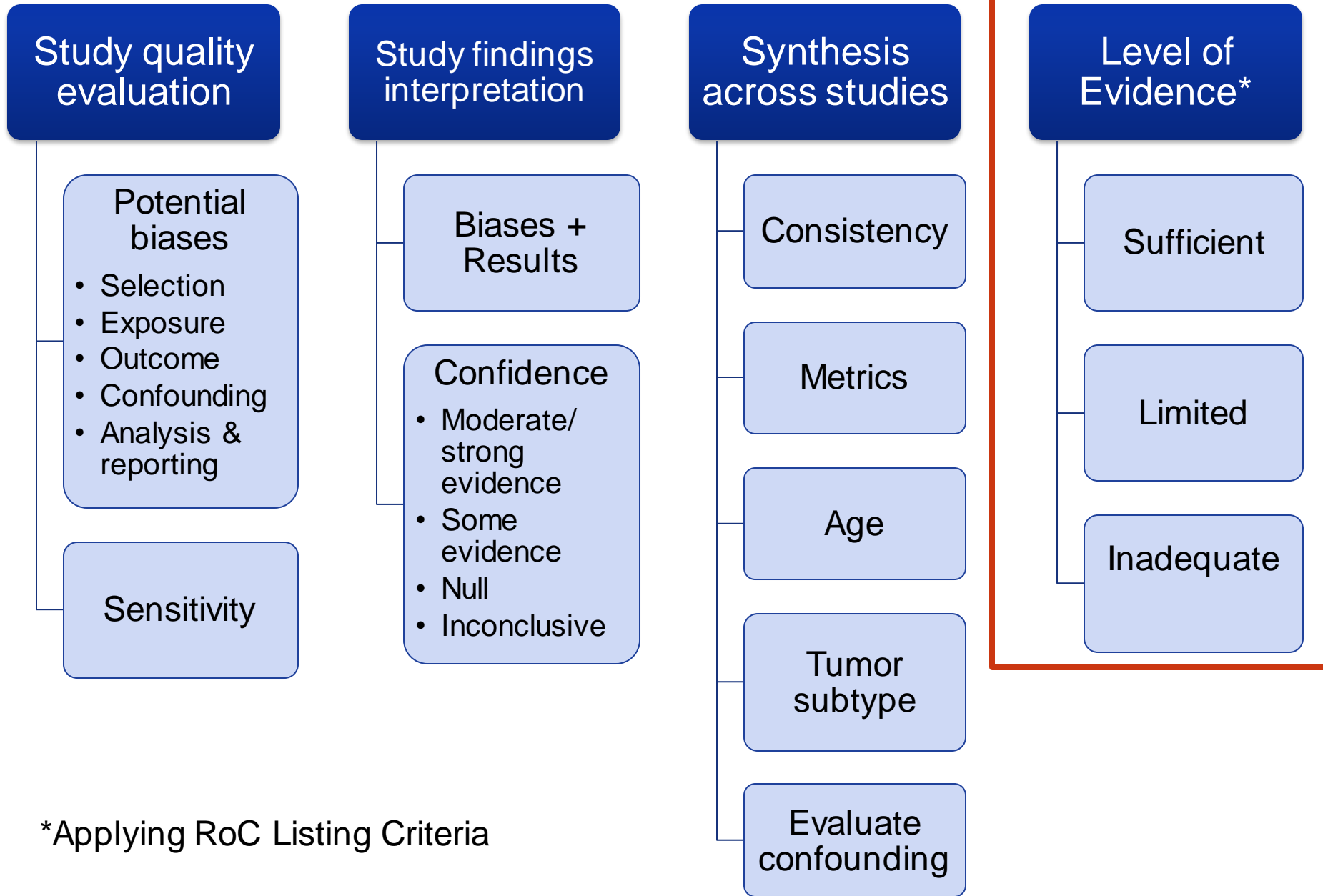
Study quality evaluation

Potential biases

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Confidence

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Synthesis across studies

Consistency

Metrics

Age

Tumor subtype

Evaluate confounding

Level of Evidence*

Sufficient

Limited

Inadequate

*Applying RoC Listing Criteria

Limited evidence: Strong

Strengths	**Limitations**
• Large database of informative studies	• Low sensitivity of most cohort studies
• Consistent findings across studies for persistent night shift work across different occupations and populations	• Low possibility of differential recall biases in case-control studies
• Potential confounding from lifestyle factors unlikely	• Possibility of co-exposure to other carcinogens in the occupational cohorts of nurses or in other populations.
• Stronger association with receptor positive breast cancer subtypes	• Two informative studies were null (Li *et al.* 2015, Vistisen *et al.* 2017).

Limited evidence: Strong but not sufficient

Strengths

- Large database of informative studies

- Consistent findings across studies for persistent night shift work across different occupations and populations

- Potential confounding from lifestyle factors unlikely

- Stronger association with receptor positive breast cancer subtypes

Limitations

- Low sensitivity of most cohort studies

- Low possibility of differential recall biases in case-control studies

- Possibility of co-exposure to other carcinogens in the occupational cohorts of nurses or in other populations.

- Two informative studies were null (Li *et al.* 2015, Vistisen *et al.* 2017).

Clarification questions?
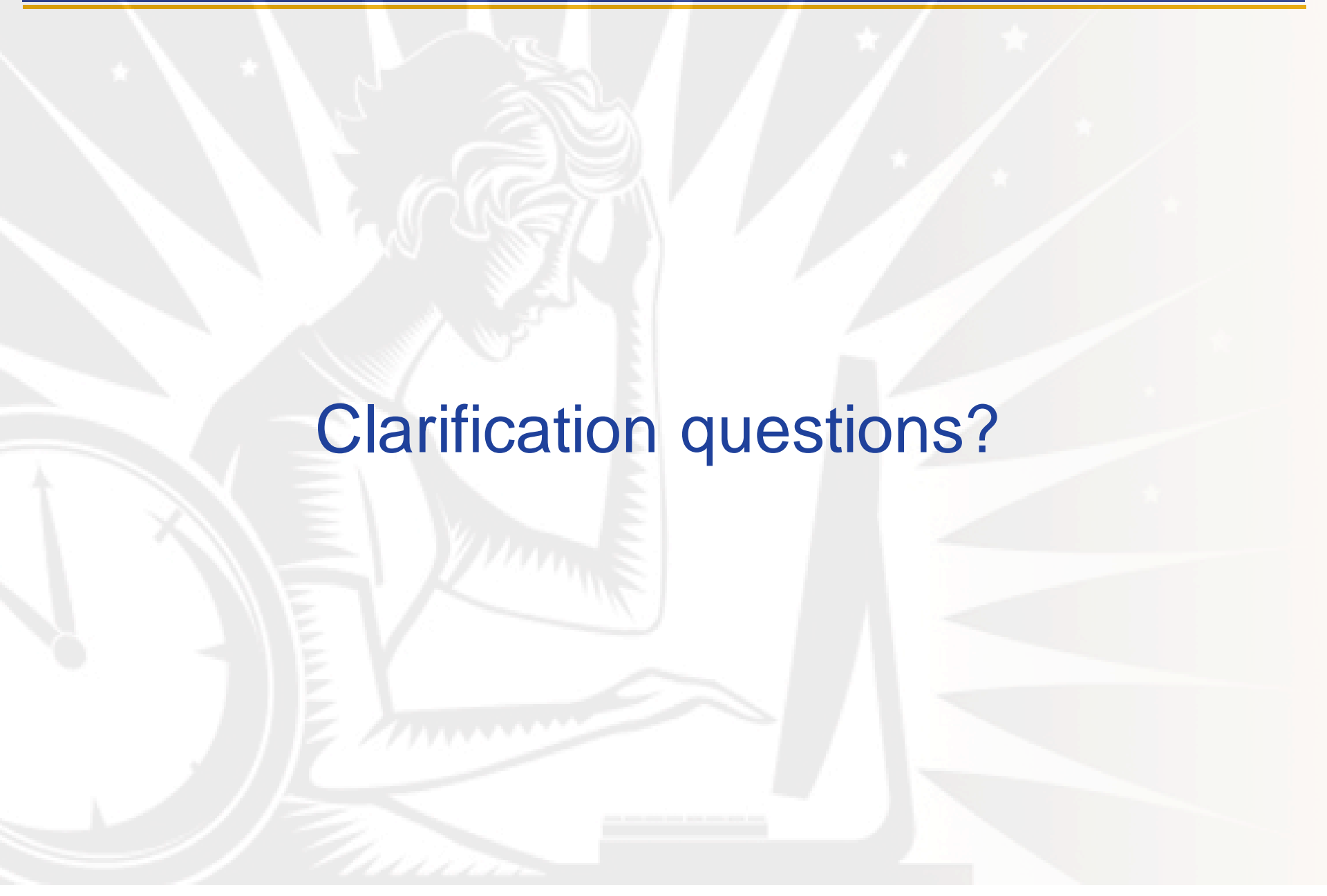
Reviewer comments

Breast cancer epidemiology

1. Comment on whether the **scientific information** is clear, technically correct, and objectively presented and identify any information that should be added or deleted

Night shift work

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2. Comment on whether the study quality evaluation (risk of bias and sensitivity to detect an effect) is systematic, transparent, objective, and clearly presented.

3. Provide any scientific criticisms of NTP's cancer hazard assessment of the epidemiologic studies.

NTP Preliminary Level of Evidence Conclusion: Vote

Limited evidence of breast cancer carcinogenicity for persistent night shift work from human epidemiology studies

- Strong but not sufficient

- Persistent defined as long-term, frequent and starting night shift work in young adulthood

Outdoor light

Indoor light - in the sleeping area

Outdoor light – studies and metrics

Outdoor light

- 3 studies used satellite images from DMSP*
- 1 study used space station photos** to develop a Melatonin Suppression Index from blue light
- 1 study used self-report of strong LAN source outside residence

*U.S. Defense Meteorological Satellite Program
** International Space Station (ISS) (Earth Science and Remote Sensing Unit, NASA Johnson Space Center (https://eol.jsc.nasa.gov)).

Metrics for outdoor LAN and results

Reference	Location	Risk Ratio	Risk Estimate	95% CI	Exp. cases
James*	U.S.		1.14	1.01 - 1.29	777
Hurley**	California		1.12	1.00 - 1.26	1041
Bauer	Georgia		1.12	1.04 - 1.20	9659
Garcia-Saenz	Spain, Blue light		1.48	1.00 - 2.17	138
Keshet-Sitton+	Israel, unspec. source		1.52	1.10 - 2.12	NR

(Risk Ratio axis: 0.5   1   2)
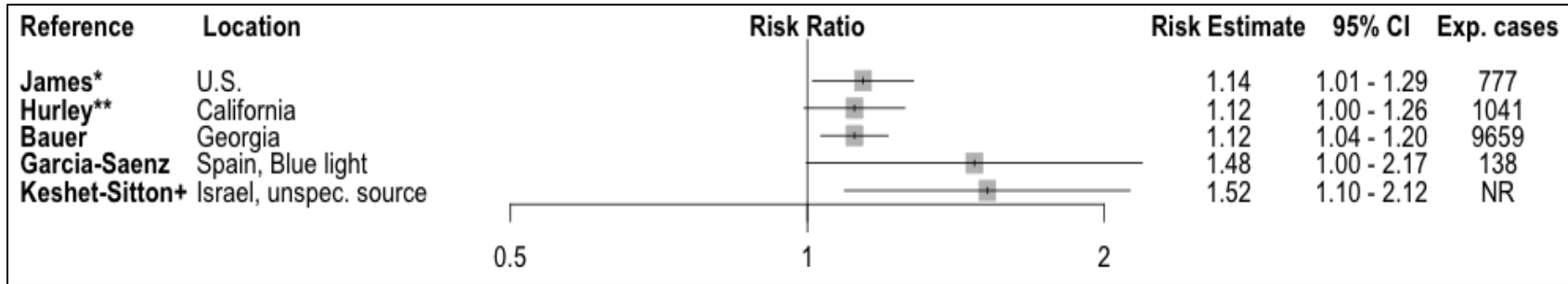
*Trend test $P = 0.02$; **Trend test $P = 0.06$. +Unspecified outdoor source of LAN; Bauer - low utility study.

- DMSP* images of LAN (3 studies)
  - higher risk among premenopausal women
  - no excess risk among post-menopausal women

- Circadian-effective metric (melatonin suppression index**) (1 study)

- Self-reported strong LAN source near residence (1 study)

- Mixed results for hormone receptor status

- 7 ecological studies report excess risk of breast cancer with high LAN

*U.S. Defense Meteorological Satellite Program (or DMSP NOAA 2015)
**International Space Station (ISS) (Earth Science and Remote Sensing Unit, NASA Johnson Space Center (https://eol.jsc.nasa.gov)).

Limited evidence of carcinogenicity

- Consistently elevated risks with higher LAN levels from moderate and high utility studies

- However,

  – Only one informative study using measure of circadian effective light reported elevated risks

  – Exposure assessment in 3 studies using satellite imagery data may not be appropriate surrogate for exposure to light that causes circadian disruption

Indoor light – Studies and metrics

Indoor light - in the sleeping area

- 10 studies with varied metrics of light in the sleeping area
- Metrics used were not specific for lux levels making comparability across studies difficult
- Limited to light while sleeping

Breast Cancer and Indoor Light at Night

Variation in metrics across studies with results

Indoor LAN metrics	Davis	Fritschi,	Garcia-Saenz	Hurley	Keshet-Sitton	Kloog	Johns	Li	O'Leary	White
	Moderate Utility						Low Utility			
High exposure										
Daytime sleeping		↑							↑	null
Subjective light: low to high	↑		null		↑	↑				
High ambient light levels	↑	↑		↑	null		null			
Frequency of non-peak sleep	↑								null	
Low to medium exposure										
Medium (20–100)	null	null		null	null		null			null
Low (5–80 lux)	null	null		↑	↑	null	null	null		null
Unclear level of exposure	Null or ↓ (1) risk with bed light or outside light (1)						Null or ↑ risk - light when waking (2), or outside light (1)			

Inadequate database

- Some studies found increased risks of breast cancer in the range of 22-70% with highest exposure in moderate utility studies

- Inconsistent results across studies

- Wide variation in metrics used to capture LAN

- Self-reported light levels subject to misclassification

- Lack of specificity of metrics

Key Issues in studies of transmeridian travel

- Small number of studies

  - 4 cohorts (5 studies) of female flight attendants with exposure data quantifying time zones crossed or international flights

- Exposure assessment challenging

  - Flight records typically do not include time zones crossed
  - Need to apply algorithms to block hours to translate to time zones crossed
  - "Flying international flights" not specific for east-west flights
  - Self-reported number of time zones crossed likely to be misclassified.

- Potential co-exposures, such as cosmic radiation, are usually highly correlated with time zones crossed

- Low sensitivity to differentiate levels of exposure which decreases study utility

Study quality and results

- In three moderate utility studies (2 in same cohort)

  – Exposure-response trend for # time zones crossed in a subgroup of women ≥3 children

- In two low utility studies, increased risks reported among women

  – Regularly flying international flights

  – Working as flight attendants for ≥15 years

  – Working as a flight attendant <25 years of age

  – Flying on high-altitude long distance flights

  – Flying more than 5,000 block hours in high-altitude long-distance flights

Inadequate database

- Moderate to strong and some evidence of increased risk of breast cancer 3 of 4 cohorts

- Small number of informative studies

- Exposure assessment challenging

- Co-exposures highly correlated with time zones crossed

Clarification questions?

Reviewer comments

Light at night

1. Comment on whether the scientific information is clear, technically correct, and objectively presented and identify any information that should be added or deleted.

2. Comment on whether the study quality evaluation (risk of bias and sensitivity to detect an effect) is systematic, transparent, objective, and clearly presented.

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Transmeridian travel

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2. Comment on whether the study quality evaluation (risk of bias and sensitivity to detect an effect) is systematic, transparent, objective, and clearly presented.

3. Provide any scientific criticisms of NTP's cancer hazard assessment of the epidemiologic studies.

NTP Preliminary Listing Recommendations

- Limited evidence of the carcinogenicity of **outdoor LAN** from human cancer epidemiology studies

  - Consistent findings of an increased risk of breast cancer in sand high exposure to outdoor LAN in studies with different designs and different populations

  - Limited number of studies and some uncertainty of exposure proxy

- Inadequate for evaluating the relationship between human breast cancer and exposure to **indoor LAN**

  - Inconsistent findings across studies

- Inadequate for evaluating the relationship between human breast cancer and exposure and **transmeridian travel**

  - Small number of studies

  - Potential confounding