NTP
National Toxicology Program

Suril Mehta, MPH
Office of the Report on Carcinogens (RoC)
National Institute of Environmental Health Sciences

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

Other human cancer studies on night shift work

- Prostate cancer
  - Background, utility of studies, assessment of findings
  - Preliminary level of evidence conclusion
- Colorectal cancer
  - Background, utility of studies, assessment of findings
- Assessment of findings
  - Female hormonal cancers (ovarian and endometrial cancers)
  - Lung cancer
- Additional studies on night shift work, LAN, transmeridian travel
- Preliminary level of evidence conclusion

Other human cancer studies on night shift work

- Prostate cancer
  - Background, utility of studies, assessment of findings
  - Preliminary level of evidence conclusion
- Colorectal cancer
  - Background, utility of studies, assessment of findings
- Assessment of findings
  - Female hormonal cancers (ovarian and endometrial cancers)
  - Lung cancer
- Additional studies on night shift work, LAN, transmeridian travel
- Preliminary level of evidence conclusion

Background

- Prostate cancer
  - Most common non-skin cancer in U.S. men
  - High survival: 98.2% of men live past five years from diagnosis[1]
  - More prevalent in older men and in African Americans

- Potential confounders
  - Age, occupational co-exposures

[1] SEER Program, 2008-2014: https://seer.cancer.gov/statfacts/html/prost.html

Quality of Prostate Cancer Studies

Key issues in night shift work studies

- Define exposure to circadian disruption (CD)
  - Crude proxies of CD are “persistent” conditions of working night shifts (e.g., long lifetime duration, high frequency of night shifts)
- Determine the most informative studies
  - Studies including metrics of “persistent” conditions of night shift work (not all studies include such metrics)
  - Low potential bias, and high or moderate sensitivity
- Consider potential effect modifiers or outcome subtypes
  - Prostate cancer severity, chronotype or sleep preference
- No quantitative meta-analysis

Overview of Prostate Cancer Studies

Reference	Location	Study type	Night work definition
Cohort studies			
Kubo et al. 2006	Japan	Population-based	Fixed and rotating, not defined
Schwartzbaum et al. 2007	Sweden	Population-based, registry	Rotating schedule or between 1:00 AM–4:00 AM
Kubo et al. 2011	Japan	Occupational cohort	Three-shift rotation
Gapstur et al. 2014	United States	Population-based	Rotating (not defined) and fixed from 9:00 PM–midnight
Hammer et al. 2015	Germany	Occupational cohort	Forward rotating
Dickerman et al. 2016	Finland	Twins cohort	Rotating shifts: rotated through morning, evening or night shifts in a two- or three-shift pattern
Åkerstedt et al. 2017	Sweden	Twins cohort	Not defined
Behrens et al. 2017	Germany	Population-based	Night work: Midnight–5:00 AM; shift work: anytime from 6:00 PM–7:00 AM
Case-control studies			
Conlon et al. 2007	Canada	Population-based	Rotating, not defined
Parent et al. 2012	Canada	Population-based	Worked from 1:00 AM –2:00 AM for ≥ 6 months
Papantoniou et al. 2015	Spain	Population-based	Midnight & 6:00 AM for ≥ 3 nights/month
Tse et al. 2017	China	Hospital-based	1+ hour between midnight & 5:00 AM
Wendeu-Foyet et al. 2018	France	Population-based	270 hours or 3 nights/month for > 1 year

- Studies vary by study design, geographic location, study type, exposure assessment method, and definition of night work

Utility of Prostate Cancer Studies

Ten studies were included in cancer hazard assessment

Reference, Location	Study design	Utility rationale	Utility
Behrens et al. 2017, Germany **Papantoniou et al. 2015,** Spain **Wendeu-Foyet et al. 2018,** France	Cohort Case-control Case-control	• Good exposure assessment • Multiple metrics • Moderate or high sensitivity • Minimal chance of selection or confounding bias	High (+++)
Conlon et al. 2007, Canada **Parent et al. 2012,** Canada	Case-control Case-control	• Moderate exposure assessment • Varying sensitivity • Lower risk of bias	Moderate (++)
Kubo et al. 2006, Japan **Kubo et al. 2011,** Japan **Hammer et al. 2015,** Germany **Åkerstedt et al. 2017,** Sweden **Tse et al. 2017,** China	Cohort Cohort Cohort Cohort Case-control	• Low exposure assessment • Low to moderate sensitivity • Potential selection bias	Low (+)
Schwartzbaum et al. 2007, Sweden **Gapstur et al. 2014,** United States **Dickerman et al. 2016,** Finland	Cohort Cohort Cohort	• Inadequate exposure assessment or sensitivity	Inadequate (0)

Assessment of Studies

Key metrics assessed and evidence evaluation

Reference	Study Utility	Key Metrics Measured in Study				
		Ever Worked	Years Worked	Work Frequency	Cancer Severity	Chronotype or Sleep Preference
Strong evidence or some evidence of prostate cancer risk						
Behrens	+++/++	***	***			***
Papantoniou	+++/++	**	***	**	***	***
Wendeu-Foyet	+++/++	Null	***	**	**	Null
Conlon	+++/++	***	**			
Parent	+++/++	***	***			
Kubo 2006	+	**				
Tse	+	*				
Null or inconclusive evidence						
Kubo 2011	+	*				
Hammer	+	Null			Null	
Åkerstedt	+	Null	Null			

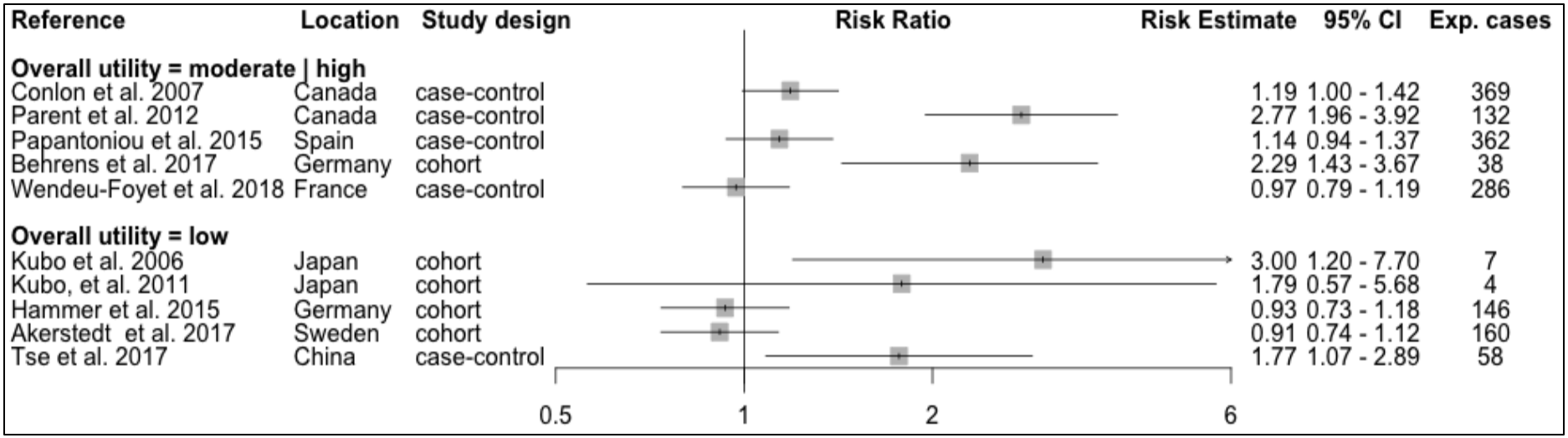
Consistent evidence across studies of an association of night shift work and prostate cancer

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

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

Prostate Cancer and Night Shift Work

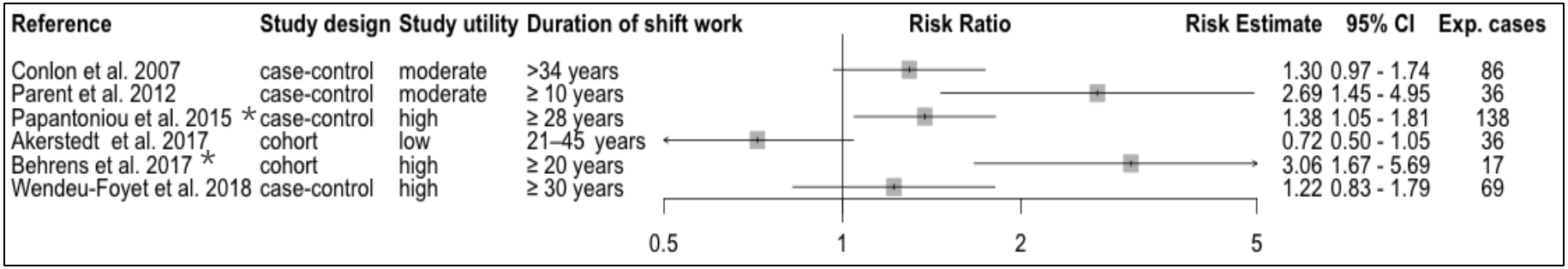
Evidence of prostate cancer risk in higher quality studies



- Four of five higher quality studies saw an increased risk of prostate cancer for having ever worked night shifts

Prostate Cancer and Night Shift Work

Longer durations of shift work associated with risk of prostate cancer; inconsistent exposure - response pattern



- Two studies showed a significant exposure-response relationship, but not consistent pattern for all studies
- Wendeu-Foyet et al. (2018) saw an increased risk with extensive permanent night shift work

* Indicates significant exposure-response relationship

Assessment of Prostate Cancer Findings

Limited evidence for prostate carcinogenicity

- Consistent findings across studies
  - Seven of ten studies of varying study designs provided evidence of an association with prostate cancer risk
  - Risk increased with a longer duration of night shift work
- Potential effect modification by prostate cancer severity
- Findings were limited by:
  - Smaller database of informative studies (n = 5)
  - Variation in exposure metrics assessed
  - Potential misclassification of shift work status in lower quality studies

Clarification questions?

Reviewer Questions

For prostate cancer:

- Comment on whether the **scientific information** is clear, technically correct, and objectively presented and identify any information that should be added or deleted.
- Comment on whether the **study quality evaluation** (risk of bias and sensitivity to detect an effect) is systematic, transparent, objective, and clearly presented.
- Provide any scientific criticisms of **NTP's cancer hazard assessment** of the epidemiologic studies.

NTP preliminary level of evidence conclusion: Vote

- **Limited** evidence for prostate carcinogenicity of night shift work from human cancer epidemiology studies
  - Positive association with persistent night shift work
  - Limited by small database of useful studies, poor characterization of night shift work exposure across studies

Other human cancer studies on night shift work

- Prostate cancer
  - Background, utility of studies, assessment of findings
  - Preliminary level of evidence conclusion
- Colorectal cancer
  - Background, utility of studies, assessment of findings
- Assessment of findings:
  - Female hormonal cancers (ovarian and endometrial cancers)
  - Lung cancer
- Additional studies on night shift work, LAN, transmeridian travel
- Preliminary level of evidence conclusion

Background

- Colorectal cancer
  - 4th most common cancer in U.S.
  - Moderate survival: 64.5% of men and women live past five years from diagnosis[1]
  - More prevalent in older age, men, and African Americans
- Potential confounders
  - Age, alcohol consumption, meat consumption, body mass index, smoking, occupational co-exposures

[1] SEER Program, 2008-2014: https://seer.cancer.gov/statfacts/html/colorect.html

Overview and Utility of Colorectal Cancer Studies

Five studies included in cancer hazard assessment

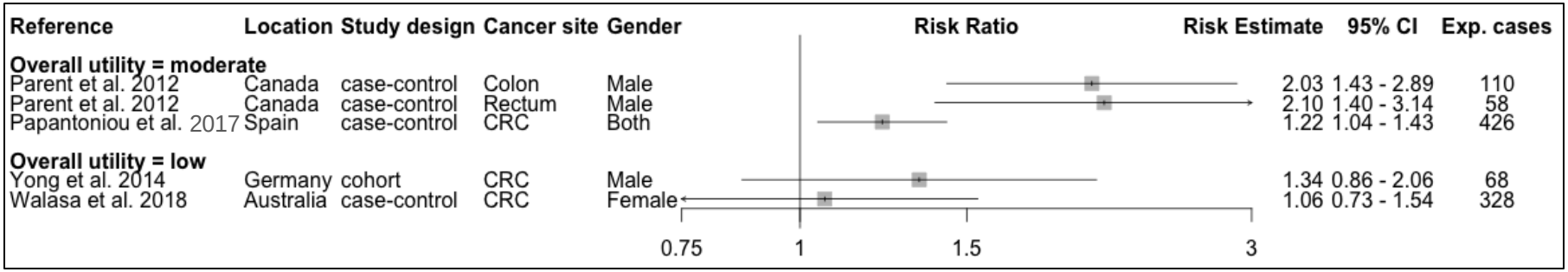
Reference, Location	Study design	Study	Utility rationale	Utility
Papantoniou et al. 2018, United States (Gu et al. 2015) [supporting study]	Cohort	Nurses' Health Studies (NHS/NHS2)	• Good exposure assessment • Multiple metrics • Moderate or high sensitivity • Minimal chance of selection or confounding bias	High (+++)
Parent et al. 2012, Canada **Papantoniou et al. 2017**, Spain	Case-control Case-control	Population-based case-control study Population-based case-control study	• Moderate exposure assessment • Moderate sensitivity • Low to moderate risk of bias	Moderate (++)
Yong et al. 2014, Germany **Walasa et al. 2018**, Australia	Cohort Case-control	Chemical workers retrospective cohort Population-based case-control study	• Low exposure assessment • Low to moderate sensitivity	Low (+)
Schwartzbaum et al. 2007, Sweden **Jørgensen et al. 2017**, Denmark	Cohort Cohort	Registry-based cohort of Swedish population Danish Nurses Organization study	• Low exposure assessment • Potential selection bias • Low sensitivity	Inadequate (0)

- Potential effect modification by gender, tumor site, smoking status, body mass index

Assessment of Colorectal Cancer Findings

Increased risk of colorectal cancer in limited number of studies

Reference	Study Utility	Key Metric Measured in Study: Ever Worked	Years Worked	Cancer Type	Gender
Strong evidence or some evidence of colorectal cancer risk					
Parent et al. 2012	+++/++	***	**	C, R	M, F
Papantoniou et al. 2017	+++/++	***	***	CRC	F
Papantoniou et al. 2018	+++/++		**	C, R, CRC	M, F
Yong et al. 2014	+	*		CRC	M
Inconclusive evidence					
Walasa et al. 2018	+	Null	*	C, R, CRC	F

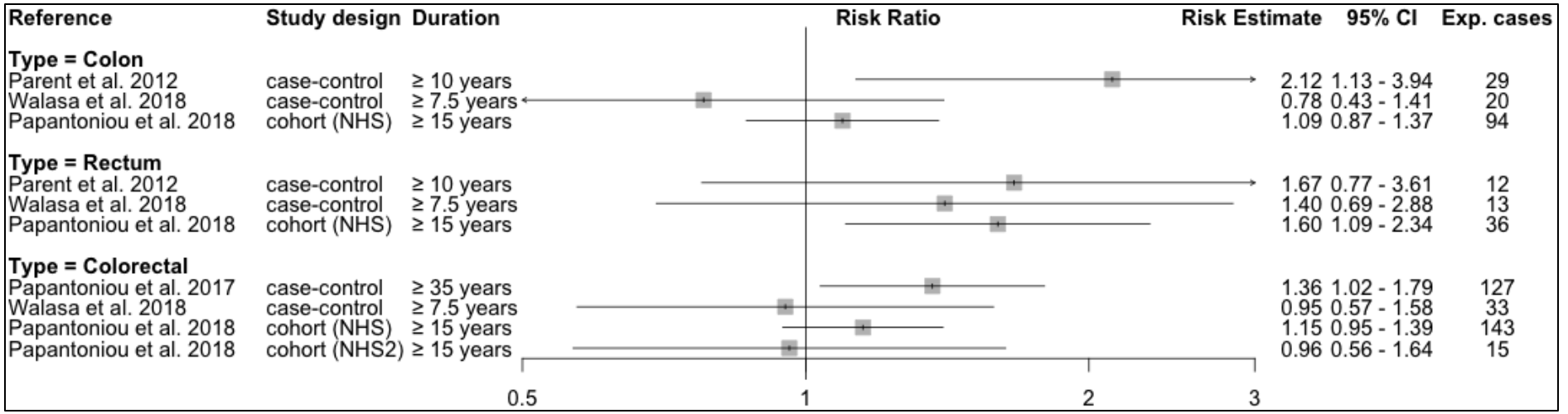


+++/++ = informative (dark yellow); + = low utility (light yellow); strength of association increases with number of * and darker shade of blue; C = Colon; R = Rectum =; CRC = Colorectal cancer; M = Male; F = Female.

Colorectal Cancer and Night Shift Work

Inconsistent evidence of increased risk with longer duration of night shift work

Reference	Study Utility	Key Metric Measured in Study: Ever Worked	Years Worked	Cancer Type	Gender
Strong evidence or some evidence of colorectal cancer risk					
Parent et al. 2012	+++/++	***	**	C, R	M, F
Papantoniou et al. 2017	+++/++	***	***	CRC	F
Papantoniou et al. 2018	+++/++		**	C, R, CRC	M, F
Yong et al. 2014	+	*		CRC	M
Inconclusive evidence					
Walasa et al. 2018	+	Null	*	C, R, CRC	F



+++/++ = informative (dark yellow); + = low utility (light yellow); strength of association increases with number of * and darker shade of blue; C = Colon; R = Rectum =; CRC = Colorectal cancer; M = Male; F = Female.

Assessment of Colorectal Cancer Findings

Inadequate database to evaluate colorectal cancer

- Most high/moderate utility studies showed an increased risk of colorectal cancer, but inconsistent results with a long duration
  - No effect modification by gender, smoking status, body mass index
  - Night shift work may differentially impact rectal cancer
- Findings were limited by:
  - Small number of informative studies (n = 3)
  - Potential confounding bias and exposure misclassification of shift work status

Other human cancer studies on night shift work

- Prostate cancer
  - Background, utility of studies, assessment of findings
  - Preliminary level of evidence conclusion
- Colorectal cancer
  - Background, utility of studies, assessment of findings
- Assessment of findings
  - Female hormonal cancers (ovarian and endometrial cancers)
  - Lung cancer
- Additional studies on night shift work, LAN, transmeridian travel
- Preliminary level of evidence conclusion

Inadequate database to evaluate hormonal cancers

- Increased risk of ovarian and endometrial cancers was seen, though not consistently in longest duration group
- Limited database
  - Only one study of endometrial cancer and two studies of ovarian cancer were of higher quality
- Poor characterization of night shift work and low to moderate study sensitivity

Lung Cancer and Night Shift Work

Inadequate database to evaluate lung cancer

- Inconsistent risk of lung cancer in having ever worked a night shift, and when stratified by duration of exposure
- Limited database from three moderate and two low utility studies
- Potential confounding: risk seen primarily among smokers
- Possible healthy worker survivor effect and variable shift work characterization

Other human cancer studies on night shift work

- Prostate cancer
  - Background, utility of studies, assessment of findings
  - Preliminary level of evidence conclusion
- Colorectal cancer
  - Background, utility of studies, assessment of findings
- Assessment of findings
  - Female hormonal cancers (ovarian and endometrial cancers)
  - Lung cancer
- Additional studies on night shift work, LAN, transmeridian travel
- Preliminary level of evidence conclusion

Other Cancer Types and Exposure Scenarios

Other cancer types and night shift work

- Elevated risk reported in studies of skin tumors, leukemia/lymphoma, stomach, and pancreatic cancers
- Inadequate number of studies for each cancer type

Other exposure scenarios

- Only one study each for LAN and transmeridian travel
- Increased risk of prostate cancer with indoor and outdoor blue LAN (Garcia-Saenz et al. 2018)
- Increased incidence of multiple cancers in airline crew members (Pukkala et al. 2012)

Clarification questions?