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National Institute of Environmental Health Sciences

Draft RoC Monograph on Night Shift Work and Light at Night
Peer Review Meeting
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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
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• Preliminary level of evidence conclusion
Prostate Cancer

Background

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

- Potential confounders
  - Age, occupational co-exposures

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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

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

- 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

<table>
<thead>
<tr>
<th>Reference, Location</th>
<th>Study design</th>
<th>Utility rationale</th>
<th>Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behrens et al. 2017, Germany</strong>&lt;br&gt;Papantoniou et al. 2015, Spain</td>
<td>Cohort&lt;br&gt;Case-control</td>
<td>• Good exposure assessment&lt;br&gt;• Multiple metrics&lt;br&gt;• Moderate or high sensitivity&lt;br&gt;• Minimal chance of selection or confounding bias</td>
<td>High (+++)</td>
</tr>
<tr>
<td>Wendeu-Foyet et al. 2018, France</td>
<td>Case-control</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Conlon et al. 2007, Canada</strong></td>
<td>Case-control</td>
<td>• Moderate exposure assessment&lt;br&gt;• Varying sensitivity&lt;br&gt;• Lower risk of bias</td>
<td>Moderate (++)</td>
</tr>
<tr>
<td>Parent et al. 2012, Canada</td>
<td>Case-control</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Kubo et al. 2006, Japan</strong>&lt;br&gt;Kubo et al. 2011, Japan&lt;br&gt;Hammer et al. 2015, Germany&lt;br&gt;Åkerstedt et al. 2017, Sweden&lt;br&gt;Tse et al. 2017, China</td>
<td>Cohort&lt;br&gt;Cohort&lt;br&gt;Cohort&lt;br&gt;Cohort&lt;br&gt;Case-control</td>
<td>• Low exposure assessment&lt;br&gt;• Low to moderate sensitivity&lt;br&gt;• Potential selection bias</td>
<td>Low (+)</td>
</tr>
<tr>
<td>Schwartzbaum et al. 2007, Sweden&lt;br&gt;Gapstur et al. 2014, United States&lt;br&gt;Dickerman et al. 2016, Finland</td>
<td>Cohort&lt;br&gt;Cohort&lt;br&gt;Cohort</td>
<td>• Inadequate exposure assessment or sensitivity</td>
<td>Inadequate (0)</td>
</tr>
</tbody>
</table>
### Assessment of Studies

## Key metrics assessed and evidence evaluation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Utility</th>
<th>Key Metrics Measured in Study</th>
<th>Ever Worked</th>
<th>Years Worked</th>
<th>Work Frequency</th>
<th>Cancer Severity</th>
<th>Chronotype or Sleep Preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong evidence or some evidence of prostate cancer risk</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Behrens</td>
<td>+++/++</td>
<td>**</td>
<td>***</td>
<td>***</td>
<td></td>
<td>***</td>
<td></td>
</tr>
<tr>
<td>Papantoniou</td>
<td>+++/++</td>
<td>**</td>
<td>***</td>
<td>***</td>
<td></td>
<td>***</td>
<td></td>
</tr>
<tr>
<td>Wendeu-Foyet</td>
<td>+++/++</td>
<td>Null</td>
<td>***</td>
<td>**</td>
<td></td>
<td>***</td>
<td></td>
</tr>
<tr>
<td>Conlon</td>
<td>+++/++</td>
<td>***</td>
<td>**</td>
<td></td>
<td>***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent</td>
<td>+++/++</td>
<td>***</td>
<td>***</td>
<td></td>
<td>***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kubo 2006</td>
<td>+</td>
<td>**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tse</td>
<td>+</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Null or inconclusive evidence

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Utility</th>
<th>Key Metrics Measured in Study</th>
<th>Ever Worked</th>
<th>Years Worked</th>
<th>Work Frequency</th>
<th>Cancer Severity</th>
<th>Chronotype or Sleep Preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kubo 2011</td>
<td>+</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hammer</td>
<td>+</td>
<td>Null</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Åkerstedt</td>
<td>+</td>
<td>Null</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Study utility</th>
<th>Duration of shift work</th>
<th>Risk Ratio</th>
<th>Risk Estimate</th>
<th>95% CI</th>
<th>Exp. cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conlon et al. 2007</td>
<td>case-control</td>
<td>moderate</td>
<td>&gt;34 years</td>
<td></td>
<td>1.30</td>
<td>0.97 - 1.74</td>
<td>86</td>
</tr>
<tr>
<td>Parent et al. 2012</td>
<td>case-control</td>
<td>moderate</td>
<td>≥ 10 years</td>
<td></td>
<td>2.69</td>
<td>1.45 - 4.95</td>
<td>36</td>
</tr>
<tr>
<td>Papantoniou et al. 2015 *</td>
<td>case-control</td>
<td>high</td>
<td>≥ 28 years</td>
<td></td>
<td>1.38</td>
<td>1.05 - 1.81</td>
<td>138</td>
</tr>
<tr>
<td>Akerstedt et al. 2017</td>
<td>cohort</td>
<td>low</td>
<td>21–45 years</td>
<td></td>
<td>0.72</td>
<td>0.50 - 1.05</td>
<td>36</td>
</tr>
<tr>
<td>Behrens et al. 2017 *</td>
<td>cohort</td>
<td>high</td>
<td>≥ 20 years</td>
<td></td>
<td>3.06</td>
<td>1.67 - 5.69</td>
<td>17</td>
</tr>
<tr>
<td>Wendeu-Foyet et al. 2018</td>
<td>case-control</td>
<td>high</td>
<td>≥ 30 years</td>
<td></td>
<td>1.22</td>
<td>0.83 - 1.79</td>
<td>69</td>
</tr>
</tbody>
</table>

- 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
• 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?
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

## Overview and Utility of Colorectal Cancer Studies

### Five studies included in cancer hazard assessment

<table>
<thead>
<tr>
<th>Reference, Location</th>
<th>Study design</th>
<th>Study</th>
<th>Utility rationale</th>
<th>Utility</th>
</tr>
</thead>
</table>
| 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 | Population-based case-control study | • Moderate exposure assessment  
• Moderate sensitivity  
• Low to moderate risk of bias | Moderate (++) |
| Yong et al. 2014, Germany | Cohort | Chemical workers retrospective cohort | • Low exposure assessment  
• Low to moderate sensitivity | Low (+) |
| Walasa et al. 2018, Australia | Case-control | Population-based case-control study | | |
| Schwartzbaum et al. 2007, Sweden Jørgensen et al. 2017, Denmark | 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
Increased risk of colorectal cancer in limited number of studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Utility</th>
<th>Key Metric Measured in Study</th>
<th>Cancer Type</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent et al. 2012</td>
<td>++++/+++</td>
<td>Ever Worked *** Years Worked **</td>
<td>C, R</td>
<td>M, F</td>
</tr>
<tr>
<td>Papantoniou et al. 2017</td>
<td>++++/+++</td>
<td>CRC</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>Papantoniou et al. 2018</td>
<td>++++/+++</td>
<td>C, R, CRC</td>
<td>M, F</td>
<td></td>
</tr>
<tr>
<td>Yong et al. 2014</td>
<td>+</td>
<td>CRC</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Walasa et al. 2018</td>
<td>+</td>
<td>Null</td>
<td>C, R, CRC</td>
<td>F</td>
</tr>
</tbody>
</table>

+++/+++ = 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.
Inconsistent evidence of increased risk with longer duration of night shift work

### Strong evidence or some evidence of colorectal cancer risk

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Utility</th>
<th>Years Worked</th>
<th>Cancer Type</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent et al. 2012</td>
<td>++++/++</td>
<td>***</td>
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<td>M, F</td>
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<td>Yong et al. 2014</td>
<td>+</td>
<td>*</td>
<td>CRC</td>
<td>M</td>
</tr>
</tbody>
</table>

### Inconclusive evidence

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Utility</th>
<th>Years Worked</th>
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<th>Gender</th>
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<tbody>
<tr>
<td>Walasa et al. 2018</td>
<td>+</td>
<td>Null</td>
<td>C, R, CRC</td>
<td>F</td>
</tr>
</tbody>
</table>

### Study Utility

+++/>++ = 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.
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

Inadequate database to evaluate colorectal cancer
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
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.

Inadequate database to evaluate hormonal cancers
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
Outline

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?