Questions

1. What is the primary study question and rationale for this investigation?
   a. What is the primary study factor (exposure)?
      Human papilloma virus (HPV)
   b. What is the primary outcome of interest? What is its significance for health?
      Cervical intraepithelial neoplasia grade 2 or 3 (CIN). CIN is a precursor lesion to cervical cancer.
   c. What is the specific issue that will be addressed and why is it important?
      The time interval between HPV detection and the development of CIN. It is important in order to strengthen the evidence that HPV infection (operationally defined here as "detection") is a cause of CIN, by demonstrating the temporal relationship between HPV and CIN. Also, knowing how quickly CIN develops following HPV will deepen understanding of the pathophysiologic process.

2. How is the study factor defined and assessed?
   The presence of HPV DNA in a cervical smear.

3. How is the outcome defined and assessed?
   Cytologic findings from the cervical smear, with histologic confirmation from a biopsy.

4. The authors use the term cumulative incidence? On what basis can they characterize their data as "incidence"?
   Incidence requires new cases. CIN found at follow-up must represent new cases (within the constraints of the accuracy of detection methods) because women had negative cytology at baseline.
5. Using the information provided in the excerpt from the Methods section, draw a detailed flow diagram showing the construction of the cohort followed in this study. To what extent is this a "fixed" cohort?

STD clinic patients, selected using a random number table → 833 patients eligible for the cross-sectional study → 779 women enrolled in the cross-sectional study → 323 met entry criteria for longitudinal study

Cohort (n=241) → 247 participants → 187 participants → 34 history of neoplasm

6 withdrawals → 60 additional patients

81 current HPV or neoplasm → 21 unsatisfactory Pap smear
6. Answer the following questions using data from the table below.

<table>
<thead>
<tr>
<th>Period (months)</th>
<th>HPV-positive/ CIN-negative women at start of period</th>
<th>CIN detected</th>
<th>Censored</th>
<th>HPV-positive/ CIN-negative women at end of period</th>
<th>Women-years of follow-up</th>
<th>Average incidence density</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12</td>
<td>110</td>
<td>17</td>
<td>25</td>
<td>68</td>
<td>89</td>
<td>0.191</td>
</tr>
<tr>
<td>13-24</td>
<td>68</td>
<td>7</td>
<td>19</td>
<td>42</td>
<td>55</td>
<td>0.127</td>
</tr>
<tr>
<td>25-36</td>
<td>42</td>
<td>0</td>
<td>14</td>
<td>28</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>37-48</td>
<td>28</td>
<td>0</td>
<td>14</td>
<td>14</td>
<td>21</td>
<td>0</td>
</tr>
</tbody>
</table>

a. Estimate the average incidence density of CIN for HPV-positive women during months 1-12.

\[
ID_{1-12} = \frac{17}{(110 - 25/2 - 17/2)} = \frac{17}{89} = 0.191/\text{year}
\]

b. Estimate the corresponding measure for HPV-positive women during months 13-24.

\[
ID_{13-24} = \frac{7}{(68 - 19/2 - 7/2)} = \frac{7}{55} = 0.127/\text{year}
\]

c. The average incidence density (ID) for HPV-positive women during months 1-24 can be estimated as the average of the answers to parts a. and b. (0.159/ year); an overall average ID_{1-24} could also be estimated as the ratio of the 24 new cases divided by the total 144 women-years of follow-up (0.167/ year). How would the overall (average) ID for months 1-48 compare to the average ID for months 1-24? What does this comparison indicate?

The average ID for 1-48 months would of course be lower, since additional follow-up time is added to the denominator but the number of new cases does not increase. This comparison indicates that intervals with very different ID’s (in this case, zero) should not be included in an overall average.

d. What would the **12-month** cumulative incidence (CI) for cervical intraepithelial neoplasia grade 2 or 3 in HPV-positive women be estimated to be if it were computed as a simple proportion (rather than using the Kaplan-Meier method, as in the article)?

12-month CI = 17 new cases / 110 women at risk = 0.154

e. What would the **24-month** CI be? How does it compare to the 12-month CI?

24-month CI = 24 new cases / 110 women at risk = 0.218; is greater than 12-month
f. What would the four-year CI be? How does it compare to the 12- and 24-month CI’s?
   4-year CI = 24 new cases / 110 women at risk = 0.218; greater than 12-month, same as 24-month

g. State the relationship among CI, ID, and follow-up time that is illustrated by the above comparisons.
   CI increases as the follow-up interval covers an increasingly larger portion of the risk period; CI is unaffected by the addition of follow-up time outside of the period of risk. ID can increase or decrease over time, so average ID for longer follow-up intervals within the risk period can be greater or smaller. Average ID is reduced by the addition of follow-up outside the risk period.

Note: An earlier version of this exercise was developed by Jo M. Harter, M.D., Ph.D.