The growing evidence behind the connection between infections and cancer (Part 2)

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This follows on from Part 1 last month
https://aonm.org/view-past-webinars/

► Breast cancer
► Monoclonal Gammopathy
► Prostate cancer

► Blood cancers
► Glioblastoma
Lung, liver, stomach and bowel the most common causes of cancer death worldwide

Source: https://www.cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer#heading-One
What cancers have infections been associated with?

Part 2:

► Lung
► Colorectal
► Gastric
► Oesophageal
► Cervical
► Liver
What cancers have infections been associated with?

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Lung cancer is the leading cause of cancer death worldwide

“Tobacco smoke ..... environmental factors such as arsenic, radon or asbestos ..... Additionally, the involvement of some viral infections such as high-risk human papillomaviruses (HR-HPVs), Merkel cell polyomavirus (MCPyV), Jaagsiekte Sheep Retrovirus (JSRV), John Cunningham Virus (JCV), and Epstein–Barr virus (EBV)”

Viral oncogenes in EBV can activate various tumour-associated pathways

Table 1. EBV gene expression in different types of latency.

<table>
<thead>
<tr>
<th>Latency Types</th>
<th>EBV Genes</th>
<th>Examples of EBV Associated Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>EBER1, EBER2, RPM1, viral miRNAs, and EBNA1</td>
<td>Memory B cells in EBV(+) individuals</td>
</tr>
<tr>
<td>I</td>
<td>EBER1, EBER2, RPM1, viral miRNAs, and EBNA1</td>
<td>Burkitt's lymphoma</td>
</tr>
<tr>
<td>II</td>
<td>EBER1, EBER2, RPM1, viral miRNAs, EBNA1, LMP1, LMP2A, and LMP2B</td>
<td>Nasopharyngeal carcinoma – Lung cancer</td>
</tr>
<tr>
<td>III</td>
<td>EBER1, EBER2, RPM1, viral miRNAs, EBNA1, EBNA2, EBNA3A, EBNA3B, EBNA3C, EBNA-LP, LMP1, LMP2A, and LMP2B</td>
<td>AIDS-associated lymphoma</td>
</tr>
</tbody>
</table>

Accumulating evidence has shown that both viral latency and lytic cycle are required for EBV pathogenesis. There are approximately 100 open reading frames encoded by the EBV genome. Among them, some latent genes such as EBV-encoded nuclear antigen 1 (EBNA1) [21], EBV-encoded nuclear antigen 2 (EBNA2), EBV-encoded nuclear antigen 3C (EBNA3C), and latent membrane protein 1 (LMP1) have been shown to mediate viral oncogenesis in cell and/or animal models. These viral oncogene products can activate various tumor-associated pathways such as Notch and nuclear factor-kB (NF-kB) signalings. In addition to well-characterized viral protein-coding genes, EBV has been shown to utilize viral non-coding RNAs (ncRNAs) such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), small non-coding EBV-encoded RNAs (EBERs), as well as recently identified circular RNA (circRNA) to facilitate its life cycle and oncogenesis [22–30].

“Both viral latency and the lytic cycle are required for EBV pathogenesis”

Chlamydia pneumoniae is significantly related to the risk of lung carcinoma

“Results showed that C. pneumoniae infection was significantly related to the risk of lung carcinoma, with a 3.19-fold increased risk compared to a negative titre (95% CI, 1.96–5.19) for IgA and 2.02 times (95% CI, 1.29–3.16) for IgG”

Chlamydia pneumoniae: “Elevated antibody titers associated with significantly increased risk”

“CHSP-60 seropositivity and elevated antibody titers were associated with significantly increased risk for subsequent lung cancer, supporting an etiologic role for C. pneumoniae infection in lung carcinogenesis.”

“Our results highlight the potential for lung cancer risk reduction through treatments targeted toward C. pneumoniae infections and chronic pulmonary inflammation.”

Source: https://aacrjournals.org/cebp/article/19/6/1498/68420/Chlamydia-pneumoniae-Infection-and-Risk-for-Lung
“One mechanism is through mediators of inflammation. Inflammation gives rise to reactive oxygen species that may cause damage to DNA. Inflammation causes cell injury, resulting in consequent cell repair, increasing the rate of cell division … higher cell turnover will increase the risk of a mutation, conferring a selective advantage to cells, leading to cancer.”

Mycoplasma infection in lung cancer was 52.6% in this study

“There was high correlation between mycoplasma infection and different cancers, which suggests the possibility of an association between the two.”

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4723534/
Mycoplasma pneumoniae infection induces reactive oxygen species and DNA damage, especially to the mitochondria

“M. pneumoniae infection induced changes in the expression of cellular proteins, in particular a group of proteins involved in the oxidative stress response, such as glucose-6-phosphate 1-dehydrogenase, NADH dehydrogenase (ubiquinone) Fe-S protein 2, and ubiquinol-cytochrome c reductase complex core protein I mitochondrial precursor ... It was further shown that M. pneumoniae infection also induced DNA double-strand breaks, as demonstrated by the formation of H2AX foci. On the other hand, an ROS scavenger, N-acetylcysteine, could inhibit the ROS generation ..”
Connections between lung cancer and SARS-CoV-2 now being investigated: vulnerability already detected

Tailored testing protocol for the possibility of infection-associated lung cancer

» Lung cancer:
1. Chlamydia pneumoniae EliSpot + IgG/IgA antibodies
2. Mycoplasma pneumoniae EliSpot + IgG/IgA antibodies
3. EBV EliSpot
What cancers have infections been associated with?

Part 2:

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- Liver
A number of bacteria implicated in the development of colorectal cancer

“Several bacteria have been identified and implicated in the development of CRC. These include: *Streptococcus bovis*, *Helicobacter pylori*, *E. coli*, *Klebsiella pneumoniae*, and more recently, *Fusobacterium*.”

... as well as several viruses: EBV, HPV, CMV and JCV

“EBV and HPV, together with cytomegalovirus (CMV or human herpesvirus type 5) and John Cunningham virus (JCV), have been consistently reported to be prevalent in CRC.”

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8978519/pdf/MOL2-16-1423.pdf
Cytomegalovirus detected in 42.3% of colorectal tumor specimens in this 2012 study

Tailored testing protocol for the possibility of infection-associated colorectal cancer

» Colorectal cancer:
1. H. pylori IgG/IgA
2. EBV EliSpot
3. CMV EliSpot
Part 2:

► Lung
► Colorectal
► Gastric
► Oesophageal
► Cervical
► Liver
Gastric cancer and H pylori/Epstein Barr Virus

“In the past decades, Helicobacter pylori and Epstein Barr virus infections have been identified and confirmed to be causal factors of gastric cancer.”

“EBV-positive gastric cancer often occurs in the proximal stomach (cardia and gastric body), where it forms lumps or ulcers that are accompanied by lymphocyte infiltration. Another noteworthy feature of EBV-positive gastric cancer is the ease of invasion into the submucosa, with a low rate of lymph node metastasis.”

EBV is the causal agent of a subset of gastric carcinomas

“The Epstein-Barr virus (EBV) is detected in the tissue of about 10% of gastric carcinoma cases throughout the world. In each case, 100% of carcinoma cells are infected with EBV. Analysis of EBV in carcinoma biopsies indicates that carcinoma is formed by the proliferation of a single EBV infected cell.”

Tailored testing protocol for the possibility of infection-associated gastric cancer

» Gastric cancer:
1. H. pylori IgG/IgA
2. EBV EliSpot
What cancers have infections been associated with?

Part 2:

► Lung
► Colorectal
► Gastric
► Oesophageal (Barrett’s Syndrome)
► Cervical
► Liver
Mycoplasma infection in oesophageal cancer was 50.9% in this study.

Table 3 Mycoplasma infection in different grades of colon carcinoma

<table>
<thead>
<tr>
<th>Grades of differentiation</th>
<th>Total number of cases</th>
<th>Negative cases (+)</th>
<th>Positive cases (+)</th>
<th>Total positive cases (+)</th>
<th>Ratio of positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-II</td>
<td>42</td>
<td>15</td>
<td>15</td>
<td>27</td>
<td>64</td>
</tr>
<tr>
<td>II-III</td>
<td>8</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>28</td>
<td>19</td>
<td>32</td>
<td>55 (mean)</td>
</tr>
</tbody>
</table>

Mycoplasma infection in other carcinoma tissues

Besides the gastrointestinal carcinomas, other cancer tissues from human esophagus, lung, breast and brain were also analyzed (Table 4).

Table 4 Mycoplasma infection in other carcinoma tissues

<table>
<thead>
<tr>
<th>Types of carcinoma</th>
<th>Total number of cases</th>
<th>Negative cases (+)</th>
<th>Positive cases (+)</th>
<th>Total positive cases (+)</th>
<th>Ratio of positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>59</td>
<td>28</td>
<td>21</td>
<td>6</td>
<td>56.9</td>
</tr>
<tr>
<td>Lung</td>
<td>59</td>
<td>28</td>
<td>23</td>
<td>8</td>
<td>55.0</td>
</tr>
<tr>
<td>Breast</td>
<td>63</td>
<td>38</td>
<td>17</td>
<td>10</td>
<td>39.7</td>
</tr>
<tr>
<td>Glioma</td>
<td>91</td>
<td>53</td>
<td>38</td>
<td>11</td>
<td>41.0</td>
</tr>
<tr>
<td>Total</td>
<td>266</td>
<td>145</td>
<td>88</td>
<td>121</td>
<td>45.5</td>
</tr>
</tbody>
</table>

Some immunoperoxidase stainings of different carcinomas are shown in Figure 1. The low differential gastric cancer (ring cell cancer) was negative reacted with PD4.
Tailored testing protocol for the possibility of infection-associated oesophageal cancer

» Oesophageal cancer:
1. Mycoplasma pneumoniae Elispot and IgG/IgA antibodies
2. H. pylori IgG/IgA
What cancers have infections been associated with?

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Chlamydia trachomatis is associated with a greater risk of invasive cervical cancer

“This study, based on data from 1,238 case and 1,100 control participants in 7 countries worldwide, shows that C. trachomatis serum antibodies were associated with a 1.8-fold increased risk of squamous cell invasive cervical cancer.”

Several independent studies suggest that HSV-2 infections correlate with a higher than normal incidence of cervical cancer, and with HPV.

“HSV infections lead to unscheduled cellular DNA synthesis, chromosomal amplifications, and mutations.”

“Among the HPV DNA-positive women, HSV-2 seropositivity was associated with increased risks of squamous-cell carcinoma.”
Tailored testing protocol for the possibility of infection-associated cervical cancer

» Cervical cancer:
1. Chlamydia trachomatis EliSpot and IgG/IgA antibodies
2. HSV I/2 EliSpot and IgG/IgA antibodies
What cancers have infections been associated with?

Part 2:

► Lung
► Colorectal
► Gastric
► Oesophageal
► Cervical
► Liver
More than half of the world’s cases of liver cancer are due to viral liver infections

“Hepatitis B virus causes cancer by integrating its DNA into human cells. Delving further, his group found that the viral break-ins led to chromosome rearrangements, wiping out genes that suppress tumours and allowing cancer cells to proliferate.”

Source: https://www.nature.com/articles/d41586-022-00821-0?proof=t
Most common risk factor for liver cancer is chronic infections with hepatitis B or C

"Individuals chronically infected with hepatitis B have a 25% to 40% lifetime risk of developing liver cancer."

Over half of cases of liver cancer – the 3rd leading cause of cancer deaths globally – are due to viral liver infections

Worldwide, the most common risk factor for liver cancer is chronic (long-term) infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). In the US, infection with hepatitis C is the more common cause of hepatocellular carcinoma, while in Asia and developing countries, hepatitis B is more common.

“Tubio’s … group found that the viral break-ins led to chromosome rearrangements, wiping out genes that suppress tumours and allowing cancer cells to proliferate.”

Campylobacter also an association: 38% of patients had liver cancer in a study of 183 patients with C. bacteremia.

“The main underlying conditions were liver disease (39%) and cancer (38%).”

Enteroviruses also associated with liver cancer

The coxsackievirus-adenovirus receptor (CAR) is “expressed more in more in liver than in other tissues ... These findings indicate that CAR plays an important role in the initiation of CVB infections and is closely associated with hepatotropism and age-specific susceptibility”.

Viral infection history can be used to detect hepatocellular cancer (HCC)

Source: https://www.cell.com/cell/pdf/S0092-8674(20)30671-1.pdf
Tailored testing protocol for the possibility of infection-associated liver cancer

» Liver cancer:
1. Hepatitis B
2. Hepatitis C
3. Camphylobacter
4. Coxsackie A/B IgG/IgA antibodies
Tailored testing protocols available for all the types of cancer mentioned

Please request from AONM (0333 121 0305)

Test panels in different cancers

- **Lung cancer**
  - Chlamydia pneumoniae Elispot & IgG/IgA antibodies
  - Mycoplasma pneumoniae Elispot & IgG/IgA antibodies
  - Epstein Barr Virus Elispot

- **Esophageal cancer**
  - Mycoplasma pneumoniae Elispot & IgG/IgA antibodies

- **Gastric cancer**
  - H. pylori IgG/IgA antibodies
  - Epstein Barr Virus Elispot

- **Colorectal cancer**
  - H. pylori IgG/IgA antibodies
  - Epstein Barr Virus Elispot
  - Cytomegalovirus Elispot

- **Cervical cancer**
  - Chlamydia pneumoniae Elispot & IgG/IgA antibodies
  - Herpes Simplex Virus (HSV) 1/2 Elispot & IgG/IgA antibodies

- **Liver cancer**
  - Hepatitis B antibodies
  - Hepatitis C antibodies
  - Campylobacter IgG/IgA antibodies
  - Coxsackie A & B IgG/IgA antibodies

31.08.2022
Further presentations on the links between pathogens and cancer available from AONM

See [https://aonm.org/cancer-webinar-series/](https://aonm.org/cancer-webinar-series/)
Professor Sapi gave us incredible insights into the possible links between Borrelia and breast cancer

https://aonm.org/view-past-webinars/
Thank you very much for your attention!

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https://aonm.org/arminlabs

or call the AONM helpline
on 0333 121 0305