A tumor profile and adapted cancer surveillance in Down syndrome

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A good knowledge of the Down syndrome tumor profile will allow

- A **good monitoring** of cancer in patients with Down syndrome,

- A better **understanding of the oncological process** in a well defined genetic condition for scientists.
The global **cancer risk in people with Down syndrome is similar to that in the general population**

Hasle et al 2000 Denmark **1.20** (CI 95% 0.92-1.55)
Patja et al 2006 Finland **0.90** (CI 95% 0.6-1.3)
Sullivan et al 2007 Australia **1.10** (CI 95% 0.68-1-68)

In the general population **one person on three** will develop a cancer during his/her life
Leukemia is currently the leading cancer in people with Down syndrome, occurring mainly during **infancy and childhood**.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Leukemia</th>
<th>Solid Trs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hasle et al 2000</td>
<td>60% (36)</td>
<td>40% (24)</td>
</tr>
<tr>
<td>Patja et al 2006</td>
<td>38% (22)</td>
<td>62% (32)</td>
</tr>
<tr>
<td>Sullivan et al 2007</td>
<td>62% (13)</td>
<td>38% (8)</td>
</tr>
</tbody>
</table>

In the general population leukemia accounts for 30% of childhood malignancies and less than 5% of adult malignancies.
### Solid tumors in children with Down syndrome

<table>
<thead>
<tr>
<th>Tumor types</th>
<th>GP</th>
<th>DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>brain-CNS</td>
<td>35%</td>
<td>possibly ↓</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>12%</td>
<td>possibly ↑</td>
</tr>
<tr>
<td>Sarcoma, bone Trs</td>
<td>11%</td>
<td>possibly ↑</td>
</tr>
<tr>
<td>Kidney</td>
<td>6%</td>
<td>↓</td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td>4%</td>
<td>↑ ↑</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>3%</td>
<td>↑ x 3-4</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>1%</td>
<td>↓</td>
</tr>
</tbody>
</table>
Brain tumors in children with DS

Brain tumors are the most frequent tumors in childhood

Even if decreased in Down syndrome they remain among the most frequent tumors

- rarity of neural tumors (medulloblastoma, PNET)
- glial tumors could occur at the same frequency?
- increase of germ cell tumors (teratoma, dysgerminoma...)

World Down syndrome Congress 2012 August 14-17 Cape Town SA
Lymphoma and Hodgkin disease in children with Down syndrome
Cases report and small series
Often appear in epidemiological studies
Could be x 2? Compared to the general population

Sarcoma and bone tumors in children with Down syndrome
Cases report and small series
Possible increase
**Germ cell tumors** in children with Down syndrome are clearly **over represented** compared to the general population.

- brain, CNS
- abdomen, retroperitoneum
- testes and ovaries
- rare in the saccroccocygeal region

**Retinoblastoma**

1 in 15,000 children in the general population could be x3-4 in Down syndrome, and occur earlier, white reflex
Cancer in women with Down syndrome

Breast

Reduced frequency in all studies 4 fold? 10 fold?
Less than 50 cases reported whereas it is the most frequent cancer in women in the general population and other intellectual disabilities.

Observed in families with increased genetic risk of breast cancer and families with genetic associated diseases favoring breast cancer.

A mode of monitoring remains to be found (increased vulnerability to X–rays) mammography? ultrasonography? palpation?
Cancer in women with Down syndrome

**Ovary**

*Increased risk* in epidemiological studies (x2?)
Adolescents dysgerminoma, adults carcinoma

**Uterine corpus**

*Increased risk* in some studies
Cases report of endometrial cancer

**Uterine cervix**

Only two cancers reported, 1 hematopoietic tumor

*Ovary and uterus cancer should be monitored as in the general population*

Uterus cervix screening to be evaluated
Cancer in men with Down syndrome

Testis

Testicular cancer is the most frequently reported malignant solid tumors in men with Down syndrome (more than 150 cases). Increased risk nearly 20 fold (1% of men cancers in the general population)
- Young adults 15-35 years
- Four times more frequently discovered at an advanced stage compared to men in the general population → treatment difficulties

A regular annual surveillance by palpation is important from 15-50 years and imaging studies if any doubt.
Digestive tract cancer in Down syndrome

(Digestive tract cancers are more frequent in people with intellectual disability).

**Esophagus**

*Reduced incidence* in epidemiological studies
Case reports

**Stomach**

*Reduced incidence* in some epidemiological studies The true frequency must be evaluated

**Colon-rectum**

*Reduced incidence* in many studies. *Increased incidence* in few studies
Probably less frequent
Digestive tract cancer in Down syndrome

**Liver**

*Increased risk* in some epidemiological studies

Hepatitis B and C are risk factors

Intrahepatic cholangiocarcinoma > hepatocarcinoma

**Gallbladder**

*clear increased risk*  x 3-8

Gallstones are risk factors

**Pancreas**

Reported in epidemiological studies despite difficulties in diagnosis. *Probably increased risk*

Digestive symptoms in adults with Down syndrome should be evaluated by *attentive physical examination followed by imaging studies* if necessary
Urinary tract cancer in Down syndrome

**Kidney**
Decreased frequency in incidence and mortality epidemiological studies

**Urinary bladder**
Decreased frequency

Urological cancers are less frequent in people with Down syndrome compared to the general population
Oropharyngeal and lung cancers in Down syndrome

Oral region

Less frequent compared to GP in epidemiological studies. Few tongue carcinoma. Reduced exposure to alcohol and tobacco.

Pharyngeal region

Idem

Lung

Very few lung cancer in various studies. Exceptional case reports.

A particular monitoring is not necessary for lung cancer. Normal clinical follow up.
Soft tissues cancer in Down syndrome

In adolescents and young adults soft tissue tumors (sarcomas) could be a little bit more frequent than in the general population. A benign tumor (lipoma, fibroma, hemangioma) may also present as a soft tissue swelling.
Brain tumors in adults with Down syndrome

Two to three fold decreased frequency of primary brain tumors in epidemiological studies. Mainly glioma, germ cell tumors and mesenchymal tumors.

Skin tumors

Malignant melanoma should be kept in mind. Case reports recently published. 3 cases at the Institut Jérôme Lejeune.
Tissues at higher risk of cancer

Hematopoietic tissue, leukemia, lymphoma. 
Gonadal germ cells, testis, ovaries, extragonadal germ cell tumors. 
Soft tissues and bone, sarcomas, bone tumors.

Tissues at lower risk

Neural tissue neuroblastoma medulloblastoma. 
Epithelial tissues (not all) breast, lung.

There is a particular constitutional vulnerability or resistance to cancer from different tissues in interaction with exogenous exposures.
Genes and cancer on 21 chromosome

**Leukemia** carcinogenesis
Genes: GATA1, ERG, ETS2, RUNX1

**Solid tumors** protecting effect
Antiangiogenic factors: COL18A1, DSCR1, DIRK1A
Antiproliferative factors: ANA (BTG3)
Differentiating agent (neural tissue): S100 Beta, PCP4
Hormonally related genes: RIP140
And many others…

The protecting genetic factors remain to be found
Cancer prevention

Physical **exercise** (overweight)
Surveillance of **gastroesophageal reflux** (esophageal carcinoma)
**_helicobacter pylori_** (gastric cancer)
Surveillance of **gallbladder lithiasis** (gallbladder cancer)
Prevention of **hepatitis B and C** (liver cancer)
Surgical correction of **testis ectopy** (testicular cancer, for clinical surveillance)
A particular situation

**Down syndrome in cancer families:** women with Down syndrome in families with higher risk of breast cancer are **not protected and should be monitored similarly to other persons in the family.**

**Down syndrome with associated genetic condition favoring cancer:** in case of tuberous sclerosis, type1 neurofibromatosis, Sturge Weber syndrome, Xeroderma pigmentosum, Cowden syndrome, **trisomy 21 did not protect against tumors favored by the associated syndrome.**
Conclusion

1) Tumors are **as frequent** in DS as in the general population with a particular **tumor profile**

2) **In children** Leukemia, lymphoma, retinoblastoma, germ cell tumors
   And any type of tumor

3) **In adults** Testicular and ovary cancer, some digestive cancers (gallbladder, pancreas, liver?)
   And any other cancers
4) In case of family cancer, similar monitoring as other family members

5) Screening
- To be established for breast cancer
- To be discussed for uterine cervix if no sexual intercourse
- To be evaluated for colon
- Important for testes, yearly palpation

6) As the prognosis of cancer depends on an early diagnosis, keep in mind the possibility of a malignancy even if it is considered as rare in Down syndrome.
ONCODEFI project Montpellier France, cancer in people with intellectual disability

Therapeutic teams
3 adults teams, 1 pediatric team
University Hospital, Anticancer Center, Mutualité clinic.

Documentation center
To gather all available data on cancer in people with intellectual disability (2000 genetic conditions associated with ID) and non genetic ID.

Research core
Epidemiology of cancer in various conditions
Psychology research, Biological research.
ONCODEFI project in Montpellier

Institut Universitaire de Recherche Clinique
Clinique de la Mutualité Beau Soleil
Centre Anticancéreux val d'Aurelle
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Thank you for your attention