Head and Neck Cancer: from genes to personalized care

Luiz P. Kowalski, MD PhD
Head and Neck Surgery and Otorhinolaryngology Department
# Recent changes in the epidemiology of head and neck cancer

Maria Paula Curado\textsuperscript{a} and Mia Hashibe\textsuperscript{b}  

*Current Opinion in Oncology* 2009, 21:194–200

## Table 1 Highest incidence rates per 100,000 for cancer of the tongue, mouth, tonsils, oropharynx, larynx and hypopharynx for men; period 1998–2002 (CI5iX)

<table>
<thead>
<tr>
<th>Registry</th>
<th>Crude rate</th>
<th>ASR(W)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tongue and mouth (C01–06)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pakistan, South Karachi</td>
<td>12.7</td>
<td>20.6</td>
</tr>
<tr>
<td>India, Trivandrum</td>
<td>14.5</td>
<td>15.3</td>
</tr>
<tr>
<td>France, Somme</td>
<td>20.0</td>
<td>15.0</td>
</tr>
<tr>
<td>France, Loire-Atlantique</td>
<td>17.7</td>
<td>13.3</td>
</tr>
<tr>
<td>Brazil, São Paulo</td>
<td>11.1</td>
<td>13.2</td>
</tr>
<tr>
<td>India, Karunagappally</td>
<td>10.9</td>
<td>12.9</td>
</tr>
<tr>
<td>France, Calvados</td>
<td>17.0</td>
<td>12.8</td>
</tr>
<tr>
<td>France, Manche</td>
<td>17.8</td>
<td>12.7</td>
</tr>
<tr>
<td>France, Bas-Rhin</td>
<td>15.4</td>
<td>11.8</td>
</tr>
<tr>
<td>India, Chennai</td>
<td>9.3</td>
<td>11.0</td>
</tr>
<tr>
<td><strong>Tonsils and oropharynx (C09–10)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France, Loire-Atlantique</td>
<td>11.4</td>
<td>8.6</td>
</tr>
<tr>
<td>France, Calvados</td>
<td>11.2</td>
<td>8.5</td>
</tr>
<tr>
<td>France, Somme</td>
<td>10.7</td>
<td>8.3</td>
</tr>
<tr>
<td>Australia, Northern Territory</td>
<td>7.4</td>
<td>7.6</td>
</tr>
<tr>
<td>France, Manche</td>
<td>10.6</td>
<td>7.3</td>
</tr>
<tr>
<td>France, Doubs</td>
<td>9.1</td>
<td>6.8</td>
</tr>
<tr>
<td>France, Bas-Rhin</td>
<td>8.4</td>
<td>6.3</td>
</tr>
<tr>
<td>France, Vendee</td>
<td>9.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Slovak Republic</td>
<td>7.1</td>
<td>6.0</td>
</tr>
<tr>
<td>USA, District of Columbia: black</td>
<td>7.0</td>
<td>5.8</td>
</tr>
</tbody>
</table>

| Larynx (C32)                                  | 25.5       | 16.1   |
| Spain, Basque Country                         | 24.7       | 15.4   |
| Spain, Zaragoza                               | 24.9       | 14.6   |
| Spain, Asturias                               | 18.7       | 14.3   |
| Spain, Murcia                                 | 21.8       | 13.7   |
| Italy, Brescia                                | 21.7       | 13.3   |
| Italy, Sondrio                                | 20.4       | 13.2   |
| Spain, Navarra                                | 17.2       | 13.2   |
| USA, District of Columbia: black              | 16.0       | 12.8   |

| Hypopharynx (C12–13)                          |            |        |
| France, Somme                                 | 13.4       | 10.2   |
| France, Manche                                | 14.9       | 9.8    |
| France, Calvados                              | 12.6       | 9.6    |
| France, Bas-Rhin                              | 10.4       | 8.0    |
| France, Doubs                                 | 10.1       | 7.3    |
| France, Loire-Atlantique                      | 8.2        | 6.1    |
| India, Chennai                                | 4.2        | 5.1    |
| France, Vendee                                | 7.4        | 5.0    |
| Slovak Republic                               | 5.7        | 4.8    |
| Croatia                                       | 7.0        | 4.8    |
RISK FACTORS FOR ORAL CANCER IN BRAZIL: A CASE-CONTROL STUDY
Eduardo L. Franco¹,², Luiz P. Kowalski², Benedito V. Oliveira³, M. Paula Curado⁴, Raimunda N. Pereira¹,
M. Estela Silva¹, Antonio S. Fava² and Humberto Torloni¹

Maté, Coffee, and Tea Consumption and Risk of Cancers of the Upper Aerodigestive Tract in Southern Brazil

Effect of Smoking Cessation and Tobacco Type on the Risk of Cancers of the Upper Aero-Digestive Tract in Brazil
Nicolas F. Schlecht¹, Eduardo L. Franco¹, Javier Pintos¹, and Luiz P. Kowalski²

FAMILY HISTORY OF CANCER IS A RISK FACTOR FOR SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK IN BRAZIL: A CASE-CONTROL STUDY
William D. Foulkes¹, Jean-Sebastien Brunet¹, Luis P. Kowalski¹, Steven A. Narod¹ and Eduardo L. Franco³,⁴

Relationship between dental factors and risk of upper aerodigestive tract cancer
A.M. Velly⁵, E.L. Franco⁶, N. Schlecht⁷, J. Pintos⁷, L.P. Kowalski⁷, B.V. Oliveira⁸, M.P. Curado⁹

Use of wood stoves and risk of cancers of the upper aero-digestive tract: a case-control study
Javier Pintos⁴, Eduardo L. Franco⁴, Luiz P Kowalski⁵, Benedito V Oliveira⁶ and Maria P Curado⁷

Interaction between Tobacco and Alcohol Consumption and the Risk of Cancers of the Upper Aero-Digestive Tract in Brazil
Nicolas F. Schlecht¹, Eduardo L. Franco¹, Javier Pintos¹, Abdissa Negassa¹, Luiz P. Kowalski² Benedito V. Oliveira³ and Maria P. Curado⁴
Lifestyle habits (tobacco, alcohol, etc.) ≠ Healthy Lifestyle
Lifestyle habits (tobacco, alcohol, etc.)

Healthy Lifestyle

CANCER

CANCER
754 cases and 1507 controls

RR for developing SCCHN:
RR = 1.97 if a first degree relative had cancer (any site)
RR = 3.65 if the relative had HN cancer
RR = 8.57 if siblings with HN cancer
RR = 2.49 if fathers had HN cancer
36 DNA samples

18 paired samples
- blood (N)
- X
- Tumor (T)

18 individuals + family history

1 first-degree relative

2 Lynch S. + HNSCC family history

1 Li-Fraumeni S. + HNSCC family history

3 laryngeal
- 5 oral cavity
- 1 oropharyngeal

Negative for mutation on mismatch repair genes

Negative for mutation in TP53
Paired Analysis

1q44 gain 7 cases OR2T6
3p12.1 loss 6 cases CADM2
7p22.3 gain 4 cases C7orf50 miR339-5p
8p23.3 loss 6 cases BCO22O82
18q23 loss 7 cases SALL3

Including family members affected by HNSCC

Case 74.1N → oropharyngeal carcinoma; uncle and brother: HNSCC; father: prostate cancer; mother: pancreatic tumor

- Loss *hsa-let-7b* (aCGH) e ↓ expressão miRNA por RT-qPCR.

Caso 65.1 → pharyngeal carcinoma; father: HNSCC; brother: lung tumor; uncle: colorectal carcinoma

- Perda sonda *hsa-let-7b* → N e T por aCGH;
- T → diminuição expressão miRNA por RT-qPCR.
• The majority of carcinogenic chemicals do not produce their biological effects per se, but require metabolic activation by host enzymes.

• Considerable amounts of tobacco and tobacco smoke are converted into DNA-reactive metabolites by cytochrome P450 related enzymes (CYP).

(Fryer and Jones, 1999).

CYP1A2*1C, CYP2E1*5B, and GSTM1 polymorphisms are predictors of risk and poor outcome in head and neck squamous cell carcinoma patients. Olivieri EH, da Silva SD, Mendonça FF, Urata YN, Vidal DO, Faria Mde A, Nishimoto IN, Rainho CA, Kowalski LP, Rogatto SR. Oral Oncol. 2009 Sep;45(9):e73-9.


• ADH3 polymorphisms - > risk for non drinkers and non smokers

• > risk for smokers and drinkers, independent on ADH genotype
**CYP1A2*1C, CYP2E1*5B, and GSTM1 polymorphisms are predictors of risk and poor outcome in head and neck squamous cell carcinoma patients**

**CYP1A2*1C, CYP2E1*5B, and GSTM1 polymorphisms are predictors of risk and poor outcome in head and neck squamous cell carcinoma patients**

Lifestyle habits (tobacco, alcohol, and genes etc.)

Healthy Lifestyle and genes

Internal carcinogen exposure → DNA damage

CANCER
Oropharyngeal Cancer Incidence Trends (age 20-44; whites)
Prevalence of HPV16+ Tumors

Hammarstedt L, et al. 
Int. J. Cancer 2006;2620-2623.

Ernster JA, et al. 
Laryngoscope 2007; online.
Fig. 2. Association of head and neck squamous cell cancer with HPV16 infection, according to cancer site and method of viral detection.
<table>
<thead>
<tr>
<th>Tumor site</th>
<th>posit./total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oropharynx</td>
<td>4/19</td>
<td>0.005</td>
</tr>
<tr>
<td>Other</td>
<td>1/73</td>
<td></td>
</tr>
<tr>
<td>Tonsil</td>
<td>3/12</td>
<td>0.0149</td>
</tr>
<tr>
<td>Other</td>
<td>2/80</td>
<td></td>
</tr>
</tbody>
</table>
Head and Neck Tumours

- The use of alcohol and tobacco can account for 70% of HN cancers (Soerjomataram et al., 2007)

- Alcohol first metabolite: Acetaldehyde

- Produced by enzymes found in normal tissue and by commensal bacteria found in the oral cavity

- Streptococci, aerobic gram-positive bacteria and fungi can produce acetaldehyde in the presence of ethanol

- Alcoholics X non-alcoholics – higher levels of *Streptococcus anginosus* in saliva (Morita et al., 2005)

- Acetaldehyde levels are 7x higher in smokers who consume alcohol
Methods

- Controls without OSCC that don’t smoke nor drink (C)
- Controls without OSCC that smoke and drink on a daily basis (SD)
- Patients with OSCC (P)

Sample Collection → DNA extraction → 16S-rDNA amplification by PCR → Amplicon Sequencing → BLAST sequences against the 16S-rDNA database: Ribosomal Database Project (1,379,424)

Ion Torrent (Applied Biosystems) 2,332,475
Most abundant bacterial phyla found

- Proteobacteria
- Firmicutes
- Bacteroidetes
- Actinobacteria
Internal carcinogen exposure and/or HPV/Bacteria?

Lifestyle habits (tobacco, alcohol, and genes etc.)

Healthy Lifestyle and genes

CANCER
Lifestyle habits (tobacco, alcohol, and genes etc.)

Healthy Lifestyle and genes

Internal carcinogen exposure and/or HPV/Bacteria?

Further genetic damage

CANCER

CANCER
TP53 Mutations in Squamous Cell Carcinoma of the Head and Neck in Brazil

R G Dorta, G Landman, L P Kowalski, J R P Lauris, M R D O Latorre & D T Oliveira

Mel-CAM (CD146) expression in parotid mucoepidermoid carcinoma

Fábio Ramôa Pires, Ine-Ming Shih, Danyel Elias da Cruz Perez, Oslei Paes de Almeida, Luiz Paulo Kowalski.

Quantitative real-time PCR ider related to prognosis in oral cancer

Differential expression of IGFBP-5 and two human ESTs in thyroid glands with goiter, adenoma and papillary or follicular carcinomas


Matrix metalloproteinase-2 and -9 activities correlate with the disease-free survival of oral squamous cell carcinoma patients

CHRISTIANE W. YORIOKA, RICARDO D. COLETTA, FABIO ALVES, INÉS N. NISHIMOTO, LUIS PAULO KOWALSKI and EDGARD GRANER.

Chromosomal Deleted Regions Defining Subsets of Head and Neck Tumors

Cristina Miracca, M.Sc., Lidia Yamamoto, B.Sc., Jontado, B.Sc., Marília de Souza Silva Takimoto, M.D., Kowalski, M.D., Ph.D., and Maria Aparecida Nagai, Ph.D.

C H R O M O S O M E 2 2 q A F R E Q U E N T S I T E O F L O S S I N H E A D A N D N E C K C A R C I N O M A

Regina C. Poli-Frederico, PhD, Nadia A. Bergamo, PhD, Patricia F. Queiroz, George Corpus, Jeremy A Squire and S of in-situ intraductal growth

DIFFERENTIAL EXPRESSION mRNAs IN SQUAMOUS CELL HEAD AND NECK: ASSOCIATION WITH GELATINASE B, AND MATRIX METALLOPROTEINASES

Mercia Medeiros Pacheco, PhD, Luis Paulo Kowalski, MD, PhD, Ines Nobuko Nishimoto, MSc, Maria Mitzi Brentani, PhD

LOSS OF IMPRINTING AND LOSS OF HETEROZYGOsITY ON 11p15.5 IN HEAD AND NECK SQUAMOUS CELL CARCINOMAS

Cláudia A. Rainho, PhD, Luiz P. Kowalski, MD, PhD, Silvia R. Rogatto, PhD
Shotgun sequencing of the human transcriptome with ORF expressed sequence tags


The contribution of 700,000 ORF sequence tags to the definition of the human transcriptome


Identification of human chromosome 22 transcribed sequences with ORF expressed sequence tags

Large-scale Transcriptome Analyses Reveal New Genetic Marker Candidates of Head, Neck, and Thyroid Cancer

Eduardo M. Reis,1,2 Elida P.B. Ojopi,1,2 Fernando L. Alberto,3 Paula Rahal,4 Fernando Tsukumo,4 Ulisses M. Mancini,5 Gustavo S. Guimarães,6 Gloria M.A. Thompson,7 Cleber Camacho,1
Elisabete Miraaca,1 André L. Carvalho,6 Abimael A. Machado,1 Apuá C.M. Paquola,1
Janete M. Cerutti,2 Aline M. da Silva,1 Gonçalo G. Pereira,1 Sandro R. Valentini,11 Maria A. Nagai,1
Luiz Paulo Kowalski,1 Sergio Verjovski-Almeida,1 Eloiza H. Tajara,1* Emmanuel Dias-Neto,1
and Head and Neck Annotation Consortium

1Departamento de Biogênica, Laboratório de Bioinformática, Instituto de Química, Laboratório de Neurociências (LI-MN), Instituto e Departamento de Patologia, and Disciplina de Oncologia, Departamento de Radiologia, Faculdade de Medicina, Universidade de São Paulo; 2Laboratórios de Fundascom Molecular, Departamentos de Medicina e Meteorologia, Universidade Federal de São Paulo; 3Departamento de Cirurgia de Cabeça e Pescoço e Ortopediatologia, Hospital do Câncer A.C. Camargo, São Paulo, SP, Brazil; 4Laboratório de Biologia Molecular e Genômica, Hemocentro e Genômica e Expressão, Departamento de Genética e Evolução, Instituto de Biologia, Universidade Estadual de Campinas, Campinas, SP, Brazil; 5Departamento de Biologia, Instituto de Biociências, Letras e Ciências Exatas, Universidade Estadual Paulista; 6Departamento de Biologia Molecular, Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto, SP, Brazil; and 11Departamento de Ciências Biológicas, Escola de Farmácia, Universidade Estadual Paulista, Araraquara, SP, Brazil

### Table 1. Genomic mapping of all ORESTES sequences and of head and neck or thyroid assembled sequences

<table>
<thead>
<tr>
<th></th>
<th>Assembled contigs + singlets</th>
<th>Percent of total</th>
<th>Genomic clusters</th>
<th>Percent of total</th>
<th>Genomic clusters colinear with RefSeqs*</th>
<th>Percent of total in each category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Containing all ORESTES†</td>
<td>173,329</td>
<td>100</td>
<td>53,105</td>
<td>100</td>
<td>33,022</td>
<td>62</td>
</tr>
<tr>
<td>Not containing head and neck or thyroid sequences</td>
<td>125,328</td>
<td>72</td>
<td>32,742</td>
<td>62</td>
<td>19,003</td>
<td>58</td>
</tr>
<tr>
<td>Containing head and neck or thyroid sequences</td>
<td>48,001</td>
<td>28</td>
<td>20,348</td>
<td>38</td>
<td>14,019</td>
<td>69</td>
</tr>
<tr>
<td>Containing only head and neck or thyroid sequences</td>
<td>23,474</td>
<td>14</td>
<td>4,186</td>
<td>8</td>
<td>2,162</td>
<td>52</td>
</tr>
<tr>
<td>Containing only head and neck sequences (normal or tumor)</td>
<td>14,815</td>
<td>9</td>
<td>2,712</td>
<td>5</td>
<td>1,396</td>
<td>4</td>
</tr>
<tr>
<td>Containing only HNSCC sequences</td>
<td>14,305</td>
<td>8</td>
<td>2,621</td>
<td>5</td>
<td>1,338</td>
<td>4</td>
</tr>
<tr>
<td>Containing only normal head and neck sequences</td>
<td>473</td>
<td>0.3</td>
<td>66</td>
<td>0.1</td>
<td>38</td>
<td>0.1</td>
</tr>
<tr>
<td>Containing only thyroid sequences</td>
<td>8,316</td>
<td>5</td>
<td>1,331</td>
<td>3</td>
<td>651</td>
<td>2</td>
</tr>
<tr>
<td>Containing only thyroid tumor sequences</td>
<td>6,591</td>
<td>4</td>
<td>1,099</td>
<td>2</td>
<td>529</td>
<td>2</td>
</tr>
<tr>
<td>Containing only normal thyroid sequences</td>
<td>1,651</td>
<td>1</td>
<td>208</td>
<td>0.4</td>
<td>106</td>
<td>0.3</td>
</tr>
</tbody>
</table>
“Despite advances in surgery, radiotherapy, and chemotherapy, the five-year survival rate for head and neck cancer has not improved significantly over the past several decades ….”
Patients with similar age, PS, ACE27, with tumor of same site, histology, stage and same treatment modality…

• Why do some patients survive and other die from cancer?
  – Treatment differences?
  – Other Patient differences?
  – Tumor biology differences?
We need!

- **Biomarkers** - characteristics that are objectively measured and evaluated as indicators of normal biologic processes, pathogenic processes or pharmacological responses to specified therapeutic interventions

We need!

- **Prognostic biomarkers** to provide information about the patients outcome, regardless of therapy
EGF-R Overexpression and Outcomes in SCCHN
Functional microarray analysis suggests repressed cell-cell signaling and cell survival-related modules inhibit progression of head and neck squamous cell carcinoma

Anna EL Coll, 1,2 Ana CQ Simoes, 3 André L Carvalho, 1 Camila M Melo, 1 Lucas Faham, 4 Luiz P Kowalski, 1 Fernando A Soares, 1 Eduardo J Neves, 4 Luiz FL Reis, 1,5 and Alex F Carvalho 1

Follow-up (months)

EGFR negative
EGFR positive
Local recurrence

- No distant disease
- Resectable tumor
- Patient performance status satisfactory

DFI>1y
  - rCSI/II
    - Salvage surgery

DFI<1y
  - rCSI/III/IV
    - EGFR-
      - Palliation? Targeted therapy?
    - EGFR+
      - Salvage surgery+targeted therapy?
We need!

- Predictive biomarkers to give information on the effect of a therapeutic intervention in a patient (and can be the targets!).
Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer.

The Department of Veterans Affairs Laryngeal Cancer Study Group

**Randomize**

- Cisplatin + 5-FU x 2
  - CR / PR → Cisplatin + 5-FU x 1 → RT
  - NR → Surgery → RT
  - Surgery
  - Radiation Therapy

NEJM Volume 324; 24: 1685-1690, 1991
# TPF toxicity Grades ≥ 3

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>60 a 83%</strong></td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td>70- 77%</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td></td>
<td>5- 22%</td>
</tr>
<tr>
<td>Mucositis</td>
<td></td>
<td>4.6 -27%</td>
</tr>
<tr>
<td>Emesis</td>
<td></td>
<td>55%</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Hitt et al. Asco 2009  
Hitt et al. J Clin Oncol 2005  
Avoid unnecessary surgical mutilation
Severe toxicity
Cost
Salvage unlikely
Signature expression as predictors for response to concomitant chemoradiotherapy in locally advanced squamous cell carcinomas of the larynx and hypopharynx.

Running title: Predictors for responsiveness in SCC of the larynx and hypopharynx

Bianca D. Barreto¹,², Olavo Feher, MD², Elier B. Cristo³, Gustavo H. Esteves³, Sarah M. Marques¹, Fernando A. Soares, M.D, Ph.D.², Alex F. Carvalho, Ph.D.¹, Diogo F. Patrão², Luiz P. Kowalski, M.D., Ph.D.², Luiz F. L. Reis, Ph.D.¹,²,³
Signature expression as predictors for response to concomitant chemoradiotherapy in locally advanced squamous cell carcinomas of the larynx and hypopharynx.

Running title: Predictors for responsiveness in SCC of the larynx and hypopharynx

Bianca D. Barreto¹,², Olavo Feher, MD², Elier B. Cristo³, Gustavo H. Esteves³, Sarah M. Marques¹, Fernando A. Soares, M.D, Ph.D.², Alex F. Carvalho, Ph.D.¹, Diogo F. Patrão², Luiz P. Kowalski, M.D., Ph.D.², Luiz F. L. Reis, Ph.D.¹,²,*
In summary

• Personalized cancer medicine must offer a better selection of cancer patients for the more effective and less toxic treatments.
266 Patients with oropharyngeal cancer, known tumor HPV status, and known number of pack-years of smoking

178 Had HPV-positive tumors
88 Had HPV-negative tumors

88 Had ≤10 pack-years
90 Had >10 pack-years
23 Had ≤10 pack-years
65 Had >10 pack-years

26 Had N0–N2a cancer
64 Had N2b–N3 cancer
15 Had T2–T3 tumors
8 Had T4 tumors

114 of 266 (42.9%) were at low risk
79 of 266 (29.7%) were at intermediate risk
73 of 266 (27.4%) were at high risk

B

Overall Survival (%)

Years since Randomization

No. at Risk
Low risk 114 111 106 102 95 46
Intermediate risk 79 70 64 54 44 24
High risk 73 52 43 33 28 8

Ang KK. N Engl J Med. 2010
# PATIENTS and METHODS

<table>
<thead>
<tr>
<th>AC Camargo Hospital</th>
<th>Barretos Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 cases</td>
<td>10 cases</td>
</tr>
</tbody>
</table>

**Neoadjuvant Chemotherapy:**
- Carboplatin + Radiotherapy

**Neoadjuvant Chemotherapy:**
- Cetuximab + Radiotherapy

**Radiotherapy**
# HPV GENOTYPING

<table>
<thead>
<tr>
<th>HPV subtype</th>
<th>AC Camargo Hospital</th>
<th>Barretos Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV16</td>
<td>16/23 (69%)</td>
<td>0/10 (0%)</td>
</tr>
<tr>
<td>HPV18</td>
<td>1/23 (4%)</td>
<td>0/10 (0%)</td>
</tr>
<tr>
<td>HPV16/18</td>
<td>1/23 (4%)</td>
<td>0/10 (0%)</td>
</tr>
</tbody>
</table>
HPV and GENE EXPRESSION ARRAY

- 6524 differentially expressed genes
- 3191 genes with up regulated expression
- 3333 genes with down regulated expression

Supervised Hierarchical Clustering

- HPV+ (18 cases)
- HPV- (15 cases)

- 798 genes differentially expressed
- 391 up regulated
- 407 down regulated

↑ SFRP4, ↑ STAG3, ↓ COL4A6, ↓ ATP6V1C2
Preliminary results

• HPV negative tumors showed less complexity and genomic instability than HPV+ tumors. Genomic losses or gains at different loci in HPV- were higher than in HPV+ cases.

• Some genes mapped on 11q13.2-q13.3 associated with progressive disease highlighted putative candidates to be validated in a large series of cases aiming to be used as molecular targets to aid in conventional therapy.
Hereditary cancer and familial aggregation: clinical and molecular profiles from Brazilian patients and their relatives with high cancer risk
Team (incito)

Coordinator: Luiz Paulo Kowalski (HACC)

Vice-coordinator: Sergio Verjovski-Almeida (IQ-USP)

Management Committee: André Lopes Carvalho (Fundação Pio XII-Barretos)
Silvia Regina Rogatto (UNESP-Botucatu)
Fernando Augusto Soares (HACC)
Samuel Aguiar Junior (HACC)
Dirce Maria Carraro (HACC)

National and International Integration

- CANADA - Montreal: McGill University
- UNITED STATES - New York: Memorial Sloan-Kettering Cancer Center
- UNITED STATES - Virginia: Virginia Bioinformatics Institute
- UNITED STATES - Houston: MD Anderson Cancer Center
- GERMANY - Heidelberg: University of Heidelberg
- FRANCE - Lyon: International Agency for Research on Cancer
- BRAZIL - Ceará: Instituto do Câncer do Ceará, Fortaleza
- BRAZIL - Paraná: Universidade Estadual de Londrina, Londrina
- BRAZIL - Mato Grosso do Sul: Universidade Federal de Mato Grosso do Sul, Campo Grande
- BRAZIL - São Paulo: Hospital A.C. Camargo, Instituto de Química da Universidade de São Paulo, Faculdade de Saúde Pública, da Universidade de São Paulo, Faculdade de Medicina da Universidade de São Paulo, Hospital de Câncer de Barretos, Barretos, Hospital Amaral Carvalho, Jau, Faculdade de Medicina, UNESP - Botucatu, Instituto de Pesquisas Energéticas Nucleares (IPEN)
- ARGENTINA - Buenos Aires: Hospital Italiano
- URUGUAY - Montevideo: VZ Grupo Colaborativo Uruguayo – Investigación de Afecciones Oncológicas Hereditárias
- PERU: Instituto Nacional de Enfermedades Neoplásicas
Training and Education Programs

Oncogenetics Course for Postgraduate Students

Oncogenetics course for nurses in the Oncology Nursing Specialization Program at HACC and developing an Oncogenetic course for a Distance Learning Format
Hereditary Cancer Syndromes and Familial Aggregation of Cancer

Screening of mutations and copy number variations (CNVs) in Hereditary Cancer Syndrome and Familial Aggregations: Colorectal Cancer - Lynch Syndrome, Breast and Ovarian Carcinoma, Li-Fraumeni Syndrome.

Investigation of mutations/SNPs that create or abrogate miRNA-binding sites in Hereditary Colorectal and Breast cancer Syndromes.

Wide genome screening for gene mutation by combining exon-enriched genomic fragment and deep sequencing in Hereditary Non-Polyposis Colorectal carcinomas.
Module B. Basic Research

Expression profile-based test for breast and prostate cancer prognosis using protein-coding and noncoding genes integrated with copy number alterations.

Integration of vascular genomics and proteomics for diagnosis and therapy of cancer.
Module C

A Phase I Study of $^{18}$F-FluoroAcetate Sodium ($^{18}$F- FAS) as a PET Imaging Agent for Tumor Detection (prostate and breast carcinoma).

Prospective nonrandomized Phase II study to identify response markers to neoadjuvant chemotherapy and association with radiotherapy and cisplatin in patients with epidermoid carcinoma of the oropharynx.
Students involved in the project

Scientific Iniciation (3)
- Marina B. Sapienza, Elisabeth Caligaro, Deborah Mundin

MSc (6)
- Sonia Nogueira, Juliana Badke, Karina Miranda, Marina Cannavan, Bruna Roz, Andrew Thomas

PhD (6)
- Francine Blumental de Abreu, Christina Haas Tarabay, Bruno Silva, Nicolle Queiroz, Juliana Lain, Maria Galli de Amorim

PosDoc (5)
- Amanda Gonçalves, Yuri José de Camargo Barros Moreira, Ana Paula W. Sampaio, Iara Ribeiro, Tiago G. Santos
Acknowledgements

Pathology
Fernando A Soares
Clovis A Pinto
Victor P Andrade
Claudia M C Camaillo

Medical Genomics Lab
Emmanuel Dias Neto
Diana Noronha
Frederico Netto
Andrew M Thomas

Neogene Lab
Silvia R Rogatto
Luciana A R Rosa
Matheus Barros Fo
Marcia Hatakeyama

Radiation Oncology
Antonio C Pelizzon

Bioinformatic Lab
Renato Puga
Leandro Lima
Fabio A Marchi

FOP Unicamp
Oslei P Almeida
Marcio A Lopes
Ricardo Colleta
Pablo Vargas
Edtard Granner

Medical Oncology
Ulysses R Nicolau
Thiabo B Silva
Andreaia G Guimarães

Chemistry Institute (USP)
Sergio V Almeida
Eduardo Reis

FMUSP/Ludwig
Luisa L Villa

Image
Rubens Chojniak
Eduardo N Lima

HSL/Ludwig
Luis F L Reis

FMUSP
Maria A Nagai
Maria M Brentani

Biobank
Antonio Hugo Silva
Dirce M Carraro

HN & ORL
José Magrin
Mauro K Ikeda
José G Vartanian
João Gonçalves Fo
Genival B Carvalho
André Y Carvalho
Renan Lira
José R Testa
Ronald N Toledo
Paula A Lorençon
Ludmilla Magrin
José C M Faria
Monica L Rodrigues
Dov C Goldenberg

Biodynamics Institute

Hospital - INCITO

Hospital A.C.Camargo