Cancer and its Causes in Korea

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Former Head of Medical Oncology at Pitié-Salpêtrière in Paris
Former President of the National Cancer Institute in France
Harm Reduction Consultant to PMI
Agenda

• Burden of Non-Communicable Diseases
• Causes of cancer in Korea
• Cancer development - a matter of dose and response
• How does cigarette smoke cause cancer
• Smoking Prevalence Globally and in Korea – Or why better, less harmful alternatives are needed
The Burden of Non-Communicable Diseases
The Burden of Non-Communicable Diseases (NCDs)

Global Burden of NCDs

NCDs such as Cardiovascular, Respiratory Disease and Cancer cause:
- > 39 Mio Death globally in 2016
- ~ 9 Mio cancer deaths in 2016

NCD Burden in Korea

NCDs such as Cardiovascular, Respiratory Disease and Cancer cause:
- > 284k death in 2016
- > 100k cancer deaths in 2016

Numbers are based on public statistics for Korea

Causes of Cancer in Korea
# Risk Factors for Cancer in Korea

**Korea, All Ages, Both Sexes, Deaths per 100,000**

<table>
<thead>
<tr>
<th>1990 rank</th>
<th>2016 rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Smoking</td>
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</tr>
<tr>
<td>2. Alcohol Use</td>
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</tr>
<tr>
<td>3. High Body Mass Index</td>
<td>3. High Fasting Plasma Glucose</td>
</tr>
<tr>
<td>4. Diet High in Sodium</td>
<td>4. High Body Mass Index</td>
</tr>
<tr>
<td>5. Diet Low in Fruits</td>
<td>5. Ambient Particulate Matter Pollution</td>
</tr>
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<td>6. Unsafe Sex</td>
<td>6. Diet High in Sodium</td>
</tr>
<tr>
<td>8. Ambient Particulate Matter Pollution</td>
<td>8. Diet Low in Milk</td>
</tr>
<tr>
<td></td>
<td>Rank 9 - 27</td>
</tr>
</tbody>
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**Numbers are based on public statistics for Korea**

Cancer development - a matter of dose response
Events in Carcinogenesis

- **Carcinogenesis Initiation Phase** (1 ~ 2 days)
  - Modified cells (Hyperplasia) appear

- **Carcinogenesis Promotion Phase** (10 ~ 20 years)
  - Adenomas appear

- **Carcinogenesis Progression Phase** (> 1 year)
  - Carcinomas appear
“What is there that is not poison? All things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison.”

Paracelsus
Dose Response

**Exposure**
“Outside” the body

**Dose**
“Inside” the body

**Response**
Change in structure or function

**Source**

**Host**

**Adverse Health Effect**

**Air, Food, Consumables**

**Humans**

**Disease**
The schematic presented here illustrates that the lower the dose, the more reduced is the response and therefore the risk associated with the response.

Adapted from: Principles of Exposure, Dose, and Response; The Johns Hopkins University, 2006
CRC Risk through intake of red and processed meat

Food: Colorectal Cancer Risk (CRC)

CRC risk through intake of Fish

Points in the figure represent median intakes in each category of consumption. Curves generated from calibrated data (solid line) and uncalibrated data (hatched line) and upper and lower confidence intervals for calibrated data (dotted lines) are shown.

Source: Norat, T; Meat, Fish, and Colorectal Cancer Risk: The European Prospective Investigation into Cancer and Nutrition DOI: 10.1093/jnci/dji164

Journal of the National Cancer Institute, Vol. 97, No. 12,
Food: Colorectal Cancer Risk (CRC)

• Red meat is classified as “probably carcinogenic” and processed meats as “carcinogenic to humans”.¹

• WCRF/AICR recommendation: Limit red meat consumption to 43 g/day, for cancer prevention.²

• So Young Kim however showed that an intake of 43 g/day of red meat⁴ lead to an increase in cancer risk in Korea

• Average consumption in Korea: ~ 109.4 g/day of red meat.³


⁴ Kim, SY; The Role of Red Meat and Flavonoid Consumption on Cancer Prevention: The Korean Cancer Screening Examination Cohort; Nutrients 2017, 9, 938; doi:10.3390/nu9090938
Cigarette Smoking and Lung Cancer: Modeling Total Exposure and Intensity; Jay H. Lubin and Neil E. Caporaso; Cancer Epidemiol Biomarkers Prev March 1 2006 (15) (3) 517-523; DOI: 10.1158/1055-9965.EPI-05-0863
How does cigarette smoke cause cancer?
Carcinogens in Cigarette Smoke

- Tobacco smoke contains more than 6000 chemicals as well as solid ultrafine particles.  
  ¹

- 93 of them have been listed by the FDA as Harmful and Potentially Harmful Constituents (HPHCs).  
  ²

- The majority are classified as carcinogens or potential carcinogens.  
  ²

¹ Rodgman A, Perfetti TA. The chemical components of tobacco and tobacco smoke 2nd ed: CRC Press, Taylor & Francis Inc (United States); 2013.
## Understanding Cancer Potency of Carcinogens*

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<tr>
<th>Carcinogens</th>
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<td><strong>Compound</strong></td>
<td><strong>IARC Class</strong></td>
<td><strong>Mean Concentration (µg/mL)</strong></td>
<td><strong>% Reduction</strong>*</td>
<td><strong>% Reduction</strong>*</td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>2B</td>
<td>4.59×10^{-2}</td>
<td>99.4% ↓</td>
<td>NR</td>
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<td>1,3 - Butadiene</td>
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BDL: Below detection limit; NR: Not reported

* compared to Tobacco Smoke

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<td>2B</td>
<td>2.55×10⁻⁰</td>
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<td>99.96% ↓</td>
<td>BDL ↓</td>
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<tr>
<td>TSNA - NNK</td>
<td>1</td>
<td>2.88×10^{-4}</td>
<td>94.3% ↓</td>
<td>99.7% ↓</td>
<td>BDL ↓</td>
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| Mean Life Time Cancer Risk* | 1 | 0.024 ↓ | 0.004 ↓ | 0.0004 ↓ |

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Cancer Potency of Carcinogens of Nicotine and Tobacco Containing Products

(Adapted from Stephens, 2017)

Based on: Stephens WE; Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke; Tobacco Control Published Online First: 04 August 2017. doi: 10.1136/tobaccocontrol-2017-053808
Example: FDA Study on IQOS Emissions

Note:
- Intense Health Canada’s Smoking Regime;
- Comparison on a per-stick basis; Excludes Nicotine, Glycerin and Total Particulate Matter

How Cigarette Smoke Causes Cancer?

Genetic damage
“the match that lights the fire”*

Carcinogens

Tumor initiation

Toxic Cigarette Emissions

Inflammation
“fuel that feeds the flames”*

Solid Ultrafine Particles**
HPHCs

Tumor progression & Invasiveness***

Cancer

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How Smoking Cessation Decreases Cancer Risk

Genetic damage
“the match that lights the fire”*

Carcinogens

Inflammation
“fuel that feeds the flames”*

Smoking Cessation

1. Reduces Genetic damage
2. Reduces Inflammation

Reduces the risk of lung cancer

Cancer

Solid Ultrafine Particles**
HPHCs

Tumor progression &
Invasiveness***

How Much Can ENDS Reduce Cancer Risk?

** Genetic damage
   "the match that lights the fire"**

** Questions**

By how much can alternative products:

1. Reduce Genetic damage?
2. Reduce Inflammation?
3. Reduce the risk of lung cancer?

** ENDS**

** Inflammation
   "fuel that feeds the flames"**

** Carcinogens**

** Tumor initiation**

** Solid Ultrafine Particles**

** Tumor progression & Invasiveness**

+ Electronic Nicotine Delivery Systems.
Smoking Prevalence Globally and in Korea — Why less harmful alternatives are needed
People will continue to smoke

- Worldwide it is estimated that more than **1 billion people** will continue to smoke in the foreseeable future.¹

- According to the ACS more than 46,700 death are attributable to smoking-related diseases every year in Korea.²

- More than 18% of the population (~33% of males) continue to smoke cigarettes in Korea.³

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² American Cancer Society: https://tobaccoatlas.org/country/south-korea/
“...new product innovations could make a lot of sense and help people transfer off cigarettes”
- Scott Gottlieb, Commissioner Food & Drug Administration

“help people to quit smoking by permitting innovative technologies that minimise the risk of harm” / “maximise the availability of safer alternatives to smoking”

“heat-not-burn, snus, moist snuff, dissolvable and inhaled nicotine may be significantly safer than cigarettes.”
- Nicky Wagner, Former Associate Health Minister

Growing number of countries are recognizing the benefit of novel smoke-free products
Scientific Update

PMI’s Evidence on IQOS related to Cancer

Prof. Manuel C. Peitsch

PMI Chief Scientific Officer
Agenda

• Totality of Evidence on IQOS to date

• Can switching to IQOS reduce genetic damage, inflammation?

• Can switching to IQOS reduce the risk of lung cancer?
Totality of Evidence on IQOS

18 Non-Clinical Studies and 10 Clinical Studies
Reduced Formation: by Disease Category

Toxic Cigarette Emissions

Exposure
- Reduced Emissions of Harmful Chemicals
- No solid ultrafine particles (PM 2.5)

Molecular changes

Disruption of biological Mechanisms
- Exposure Reduction in IQOS users
- Effect on By-Standers

Cell/Tissue Changes

Disease
- Incidence of Lung Carcinomas in animal model significantly reduced

Population Harm

Reduced Emissions

Reduced Exposure

Reduced Adverse Health Effects

PMI
How Cigarette Smoke Causes Cancer?

Carcinogens

Genetic damage
“the match that lights the fire”*

Questions

Does switching from cigarettes to IQOS

1. Reduce Genetic damage?
2. Reduce Inflammation?
3. Reduce the risk of lung cancer?

Inflammation
“fuel that feeds the flames”*

Solid Ultrafine Particles**
HPHCs

Tumor progression & Invasiveness***

Cancer

Tumor initiation

Genetic damage


Genetic Damage is Reduced by IQOS

Does Switching to IQOS Reduce Genetic damage?

Evidence from IQOS Assessment

Reduced Emission of Carcinogens

Reduced Exposure to Carcinogens

Reduced Genotoxicity

Reduced DNA Damage

Reduced Genetic Damage

Genetic damage
“the match that lights the fire”*

Carcinogens

Tumor initiation

Levels of Harmful Chemicals Significantly Reduced For IQOS

Average reductions in **emission** of harmful or potentially harmful constituents for IQOS compared to levels measured in smoke from the 3R4F reference cigarette by disease category*

KFDA’s analysis of the HNB aerosol also confirmed the on average 90% lower levels of harmful chemicals in the HNB aerosol compared to cigarette smoke.

*Aerosol collection with Intense Health Canada’s Smoking Regime (55 mL puff volume, 2 second puff duration, 30 second interval puff); Comparison on a per-stick basis Reduction calculations exclude Nicotine, Glycerin and Total Particulate Matter
The PMI 58 list includes the FDA 18,and the 15 carcinogens of the IARC Groups 1
Reduced Exposure To Carcinogens

The highest-ranking carcinogens for cigarettes are 1,3-butadiene and acrylonitrile, accounting for more than three-quarters of the cancer potency…..

Stephens WE; Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke; Tobacco Control Published Online First: 04 August 2017. doi: 10.1136/tobaccocontrol-2017-053808
Genetic Damage is Reduced by IQOS

Perturbation of the DNA damage response network of the nasal epithelium in the Apoe^-/- mouse switching study.

Note: the “switch to IQOS” and “Switch to cessation” study groups were exposed for 2 month to 3R4F cigarette smoke prior to being switched.

Inflammation is Reduced by IQOS

Evidence from IQOS Assessment

Reduced Emission of HPHCs and No Solid Ultrafine Particles

- Reduced Exposure to HPHCs
- No Exposure to Solid Ultrafine Particles

Tumor progression & Invasiveness

Reduced Exposure to HPHCs and No Solid Ultrafine Particles

Reduced Lung Inflammation

Inflammation

“fuel that feeds the flames”*

Solid Ultrafine Particles**

HPHCs

Does Switching to IQOS Reduce Inflammation?

Reduced Inflammation

Solid Ultrafine Particle Deposition in the Lung

Cigarette Smoke
Solid Ultrafine Particles
$6 \times 10^{11}$ particles $\sim 0.7$ mg

IQOS Aerosol
No Solid Ultrafine Particles

Lung Deposition after 6 months

Cigarette smoke*

IQOS aerosol*

* Corresponding nicotine concentrations

Apoe-/- mice exposed for 6 months, 3h/day and 5days/week.
No Lung Inflammation in IQOS Exposed Mice

Total Cell Count in BALF

MMP Activity in BALF

T-Lymphocyte Count in BALF

Neutrophil Count in BALF

Source: PMI Study Report of Study - Study number 15020
How Cigarette Smoke Causes Cancer?

Genetic damage
“the match that lights the fire”*

Inflammation
“fuel that feeds the flames”*

Questions
Does switching from cigarettes to IQOS

1. Reduce Genetic damage? ✓
2. Reduce Inflammation? ✓
3. Reduce the risk of lung cancer?

Carcinogens

Solid Ultrafine Particles*
HPHCs

Tumor initiation

Cancer

Tumor progression & Invasiveness***

Lung Cancer Study - Design

26.8 µg/L nicotine concentration in IQOS aerosol represents 56 Sticks/day*

**Study Groups**

- **Female A/J mice**
  - Air: 0 µg/L, n = 75
  - 3R4F: 13.4 µg/L, n = 75
  - IQOS Low: 6.7 µg/L, n = 74
  - IQOS Medium: 13.4 µg/L, n = 75
  - IQOS High: 26.8 µg/L, n = 72

- **Male A/J mice**
  - n = 118

**Interim dissections**

n = Number of animals at months 18 assessable for carcinoma incidence.

26.8 µg/L nicotine concentration in IQOS aerosol represents 56 Sticks/day*


Stinn et al., 2013, Toxicology. 2013, 305:49-64. doi: 10.1016/j.tox.2013.01.005
Incidence and Multiplicity of Lung Carcinoma

Incidence and multiplicity of Lung Carcinomas are significantly increased upon exposure to 3R4F smoke compared to air exposure.

Source: PMI Study Report of Study - Study number 15020
Incidence and Multiplicity of Lung Carcinoma

Incidence of Lung Carcinoma

Multiplicity of Lung Carcinoma

Incidence and multiplicity of Lung Carcinomas in IQOS exposed mice was significantly lower compared to 3R4F smoke exposed mice and similar to air exposed mice.

Source: PMI Study Report of Study - Study number 15020
Conclusions

• IQOS reduces genetic damage compared to continued smoking

• IQOS reduces inflammation compared to continued smoking

• IQOS reduces incidence and multiplicity of lung adenomas and lung carcinomas in a validated cancer animal model
Risk Assessment Model

Toxic Cigarette Emissions

Exposure ➔ Molecular changes ➔ Disruption of biological Mechanisms ➔ Cell/Tissue Changes ➔ Disease ➔ Population Harm

Reduced Emissions ➔ Reduced Exposure ➔ Reduced Adverse Health Effects

PMI

- Reduced Emissions of Harmful Chemicals
- No solid ultrafine particles (PM 2.5)

- Exposure Reduction in IQOS users
- Effect on By-Standers

- Incidence of Lung Carcinomas in animal model significantly reduced
What We Know Today

• IQOS is not risk free and is addictive and the best choice is to quit
• Smokers carry a time-dependent relative risk of disease based on their smoking history when they quit or switch to IQOS
• IQOS is a much better choice for smokers than to continue smoking cigarettes

• We all share the responsibility to provide accurate information based on sound science
• Consumers have the right to receive accurate and non-misleading information to make an informed, better choice for their health
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