Individuals often avoid any consideration of cancer until diagnosis.

This presentation will focus on cancer from the perspective of airline pilots.

Current strides in cancer research will also be reviewed.
Presentation Outline

- What Cancer is and is NOT
- Genetics and Epigenetics
- Hereditary vs. Non-Hereditary
- Environmental Risks
  - Occupational
  - Dietary
- Research - My Part
- Prevention and Early Detection - Your Part
I. What Cancer IS and is NOT

Cancer IS a collection of cells that:

- have an abnormal increase in cell division
- lose specific cell features & functions
- ultimately invade and spread to other tissues

If not stopped, cancer robs the body of nutrients leading to organ failure and death.
I. **What Cancer is and is NOT**

Cancer is NOT:

- a benign tumor (though some can progress to cancer)
- wholly unpreventable
- unbeatable

If stopped or slowed, individuals with cancer can live a relatively long life with a reasonable quality of life
I. What Cancer is and is NOT

In general, cancer is a genetic disease.

genes change → cells change → cancer develops
II. Genetics and Epigenetics

What are genes?

- region of DNA that controls a hereditary characteristic
- working DNA subunits - information for making proteins
- there are about 22,000 human genes

Exon 1 – makes 1st part of protein; Exon 2 makes 2nd part of protein, etc.
Introns – intervening sequences that can regulate gene expression
II. Genetics and Epigenetics

Chromosome 19 has about 300 identified genes.

Genes make up about 2% of the total DNA in chromosomes.
II. Genetics and Epigenetics

How do genes change?

- deletion
- point mutation
- duplication
- inversion
- insertion
- translocation
II. Genetics and Epigenetics

- Increased chromosome translocations in airline pilots with long-term flying experience
  - association between translocation frequency and flight years (n=83 airline pilots)
  - largest study of its kind
  - total number of participants (n) is still rather low

From the National Institute for Occupational Safety and Health in Cincinnati, OH.
II. Genetics and Epigenetics

Point Mutations at the Base Pair Level
II. Genetics and Epigenetics

What causes genes to change?

1. inheritance – altered genes

2. other disorders – chronic diseases, viral infection, inflammation
   - colitis, IBD → colon cancer
   - pancreatitis → pancreatic cancer

3. carcinogens – smoking, UV radiation

4. diet – obesity, fat intake, total calories

Last two are epigenetic phenomena
II. Genetics and Epigenetics

Epigenetics

Something above and beyond normal gene regulation that alters gene expression

Example:
Higher rates of cancer associated with: cigarette smoking and high fat diets
II. Genetics and Epigenetics

• Cancer involves genetic mutations

• Altered gene expression/protein function:
  1. higher level/increased activity
     similar to the accelerator of a car
     (oncogenes or growth factors)
  2. lower level/lost activity
     similar to a car brake
     (tumor suppressor genes)

• Combination of genetic changes drive normal cells to cancer cells
II. Genetics and Epigenetics

Individual genes vs. a genetic “circuit”

Combination of genetic changes drive normal cells to cancer cells
II. Genetics and Epigenetics

As an example, in pancreatic cancer:

- higher expression & altered activity –
  mutant Kras = stuck accelerator

- lost expression & no activity –
  p16 = broken brake
II. Genetics and Epigenetics

How normal cells “crash” into cancer cells
II. Genetics and Epigenetics

- The Bottom Line:
  - Random genetic change, through a mistake in normal gene processing or induced by an epigenetic event, can trigger other genetic alterations
  - A combination of these genetic mutations can induce cellular changes
  - Multiple cellular changes can generate cancer
III. Hereditary vs. Non-Hereditary

- Like normal genes, mutated genes can be inherited
- A single altered gene ≠ cancer, rather a higher incidence of certain cancers
- Some genes are more critical than others particularly TSGs, where loss leads to a syndrome
  example: p53 loss = Li-Fraumeni Syndrome
III. Hereditary vs. Non-Hereditary

- 1-2% of all cancers are hereditary
  - seems relatively low

- any given gene mutation = increased risk for cancer
  - loss of p53 is common to many types of cancers

- Table of Familial Cancer Syndromes
  online article: Dr. Paolo Radice Istituto Nazionale Tumori, Milano, Italy
<table>
<thead>
<tr>
<th>Clinical syndrome</th>
<th>Neoplasm</th>
<th>Gene</th>
<th>Product location/Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial adenomatous polyposis</td>
<td>Colon</td>
<td>APC</td>
<td>Cytoplasm/cell adhesion</td>
</tr>
<tr>
<td>Neurofibromatosisist Type 1</td>
<td>Pheripheral neurofibromas</td>
<td>NF-1</td>
<td>Cytoplasm</td>
</tr>
<tr>
<td>Neurofibromatosis Type 2</td>
<td>Schwannomas, gliomas</td>
<td>NF-2</td>
<td>Inner cell adhesion</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia 1</td>
<td>Pituitary, pancreas, parathy thyroid,</td>
<td>?</td>
<td>?/?</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia 2</td>
<td>phaeochromocytoma</td>
<td>RET</td>
<td>Membrane/TKR</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>Sarcomas, breast cancers</td>
<td>TP53</td>
<td>Nucleus/Transcription</td>
</tr>
<tr>
<td>Von Hippel Lindau disease</td>
<td>Haemangioblas, renal cell</td>
<td>VHL</td>
<td>Membrane?/?</td>
</tr>
<tr>
<td>Familial retinoblastoma</td>
<td>Retinoblastoma, sarcomas</td>
<td>RB</td>
<td>Nucleus/Transcription</td>
</tr>
<tr>
<td>WAGR syndrome</td>
<td>Wilms tumors</td>
<td>WT1</td>
<td>Nucleus/Transcription</td>
</tr>
<tr>
<td>Familial melanoma</td>
<td>Melanomas</td>
<td>CDKN2</td>
<td>Cytoplasm</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>Lymphomas, breast</td>
<td>MTS1</td>
<td>Cell cycle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ATM</td>
<td>cell cycle control ?</td>
</tr>
</tbody>
</table>
III. Hereditary vs. Non-Hereditary

Genetic Susceptibility

1. Sporadic - account for 85-90%
2. Familial - account for <10%
3. Genetic Syndromes - 3-5%
III. Hereditary vs. Non-Hereditary

- Some cancers have lower hereditary risk
  (like lung and cervical cancers)

- Other cancers have higher hereditary risk
  (like colon and breast cancers)

- Majority are sporadic cancers
  - develop from mutations induced by carcinogens or other stimuli (derived from epigenetic events)
Can anything be done with inherited genes?

ABSOLUTELY!
Pay attention to your family tree
- Two or more blood relatives with same type of cancer
- Certain cancers at young age
- Two types of cancers in the same blood relative
- National descents/high risk groups

In these cases, you should: (1) enroll in an early screening program (2) may need to seek genetic counseling.
Practical Application

- Can anything be done with non-hereditary issues?

OF COURSE!

Pay attention to your environment (epigenetic factors)
- exposure to carcinogens
- diet
- severe lifestyle disruptions
More specific risks for airline pilots
IV. Environmental Risks

- Anything outside of genes and inheritance
  - Occupational Risks = potential long-term exposure to
    1. carcinogen(s) = UV light, radiation
    2. adverse stimuli = stress, changes in circadian rhythm
  - Diet = increased intake of high fat, high sugary foods
  - Other = non-work related stress and exposures
IVa. Occupational Risks: Carcinogens

- UV light & cosmic radiation
  - 50 times greater exposure than those in the general population
  - within limits of radiation workers
  - a lifetime increase in cancer at ~1%

All of this is correlated with high-altitude, high-latitude routes

Dr. Robert J. Barish, medical radiation specialist & author
IVa. Occupational Risks: Radiation

- Radiation
  - limit = 2,000 mrem/yr  
    (recommended by ICRP & FAA)
  - 600 mrem/yr  
    (recommended by NRCP)

- annual dose for an airline pilot = 200-500 mrem/yr  

- average dose is ~220/yr  
  (Aviat Space Environ Med 69(7):621-5; 1998)
IVa. Occupational Risks: Radiation

- Radiation Exposure Rates
  - Seattle to Portland: 3 mrem per 100 block hours
  - New York to Chicago: 39 mrem per 100 block hours
  - Los Angeles to Honolulu: 26 mrem per 100 block hours
  - London to New York: 51 mrem per 100 block hours
  - Athens to New York: 63 mrem per 100 block hours
  - Tokyo to New York: 55 mrem per 100 block hours

Health Phys 79(5):591-5; 2000
IVb. Occupational Risks: Stress (Psychological)

- The role of stress in cancer development
  - poorly understood
  - difficult to measure (humans) or induce (models)
  - changes in hormones and/or endorphins may contribute (depending on the type of cancer)
  - many individual differences
  - most studies show that cancer causes stress

There is no conclusive evidence that associates stress with the induction of cancer

Rev Epidemiol Sante Publique. 2009 Apr;57(2):113-23
IVc. Occupational Risks: Chronodisruption

- Changes in Circadian Rhythm
  - an internal biological clock
  - regulates biological processes during a 24-hour period

- Chronodisruption (CD)
  - affects physiology, metabolism, and behavior
  - increased cancer risk with frequent CD
IVc. Occupational Risks: Chronodisruption

- Melatonin
  - Hair growth and skin pigmentation
  - Antioxidant and free radical scavenging activity
  - Suppresses ultraviolet (UV)-induced damage
  - A critical factor in internal time-keeping
  - Biomarker of circadian dysregulation
  - Both pro-oncogenic & anti-oncogenic properties
    (colon & prostate) (melanoma & lymphoma)

Endocrine. 2005 Jul;27(2):137-48
Endocrine, vol. 27, no. 2, 137–147
IVc. Occupational Risks: Chronodisruption

- melatonin lower in the day & higher at night
- number of nights worked $\sim \frac{1}{\text{urinary melatonin levels}}$
- prolonged light may reduce melatonin secretion

Example:

In melanoma-bearing mice:
1. exogenous melatonin decreased tumor volume/weight
2. increase light cycle enhanced tumor progression & malignancy

Cancer Epidemiol Biomarkers Prev. 2008 Dec;17(12):3306-13
IVc. Occupational Risks: CD & UV radiation

- A Combination of CD and UV radiation
  - CD = reduced levels of melatonin (less protection)
  - UV = increased exposure to radiation (above average)

This might explain 2-3 fold increase in melanoma, particularly in airline pilots on high altitude/latitude routes

Ultimately, additional factors may add to this risk
IVd. Diet

- High fat diets
  - increase UV-induced skin tumors in rodent systems
  - low fat diet reduced these effects

  Mutat Res. 1998 Nov 9;422(1):185-90

- Unclear if this trend is significant in humans
  - high alcohol consumption increased risk for melanoma
  - increased fat did not seem to affect cancer development
  - yet, increased PUFA further modified the risk in cohorts with high alcohol consumption

  Am J Epidemiol. 2006 Aug 1;164(3):232-45
IVe. Non Occupational Risks

- Additional sun exposure
- Increased alcohol consumption
- High caloric/high fat diet (esp. in combination with above)
- Cigarette smoking
- Excess traveling – further Chronodisruption
- High psychological stress levels
IV. Occupational Risks

- Caveats for Consideration
  - lower than average mortality rate (good news!)
  - near-average cancer incidence rate (overall)
  - general good health with frequent check-ups
  - relatively small group (compared with other lines of work)
  - very good record keeping (flight hours, etc.)

- These bode well for epidemiological studies
  (The case can be made that more of this should be done)
IV. Environmental Risks

- Increased rate in skin cancer:
  - melanoma = 2.3-fold
  - squamous cell cancer = 2.1-fold
  - basal cell carcinoma = 2.5-fold (over 10,200 pilots)

- Increased rate in leukemia?
  - One study showed an increase in CLL*
  - Another showed an increase in AML
  - A third showed no increase in any leukemia

* Radiat Environ Biophys. 2004 Feb;42(4):247-56
### IV. Environmental Risks

<table>
<thead>
<tr>
<th>Cancer sites (ICD-7)*</th>
<th>Obs</th>
<th>Exp</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers (140-205)</td>
<td>23</td>
<td>23.68</td>
<td>0.97</td>
<td>0.62 to 1.46</td>
</tr>
<tr>
<td>Oesophagus (150)</td>
<td>1</td>
<td>0.36</td>
<td>2.78</td>
<td>0.04 to 15.45</td>
</tr>
<tr>
<td>Colon (153)</td>
<td>1</td>
<td>1.57</td>
<td>0.64</td>
<td>0.01 to 3.54</td>
</tr>
<tr>
<td>Gall bladder (155.1)</td>
<td>1</td>
<td>0.12</td>
<td>8.33</td>
<td>0.11 to 46.36</td>
</tr>
<tr>
<td>Lung (162)</td>
<td>2</td>
<td>3.13</td>
<td>0.64</td>
<td>0.07 to 2.31</td>
</tr>
<tr>
<td>Prostate (177)</td>
<td>5</td>
<td>3.91</td>
<td>1.28</td>
<td>0.41 to 2.98</td>
</tr>
<tr>
<td>Kidney (180)</td>
<td>2</td>
<td>1.41</td>
<td>1.42</td>
<td>0.16 to 5.12</td>
</tr>
<tr>
<td>Malignant melanoma - skin (190)</td>
<td>5</td>
<td>0.49</td>
<td><strong>10.20</strong></td>
<td>3.29 to 23.81</td>
</tr>
<tr>
<td>Eye (192)</td>
<td>1</td>
<td>0.10</td>
<td>10.00</td>
<td>0.13 to 55.64</td>
</tr>
<tr>
<td>Brain (193)</td>
<td>2</td>
<td>1.14</td>
<td>1.75</td>
<td>0.20 to 6.33</td>
</tr>
<tr>
<td>Thyroid (194)</td>
<td>1</td>
<td>0.67</td>
<td>1.49</td>
<td>0.02 to 8.30</td>
</tr>
<tr>
<td>Unspecified sites (199)</td>
<td>1</td>
<td>0.49</td>
<td>2.04</td>
<td>0.03 to 11.35</td>
</tr>
<tr>
<td>Leukaemia (204)</td>
<td>1</td>
<td>0.59</td>
<td>1.69</td>
<td>0.02 to 9.43</td>
</tr>
<tr>
<td>Acute myeloid leukaemia (204)</td>
<td>1</td>
<td>0.26</td>
<td>3.85</td>
<td>0.05 to 21.40</td>
</tr>
</tbody>
</table>

Occup Environ Med. 2000 Mar;57(3):175-9
### IV. Environmental Risks

**Table 6: Number for all cancers (skin, eye, and leukaemia) among 256 Icelandair pilots according to whether ever flying over five time zones**

<table>
<thead>
<tr>
<th>Cancer sites (ICD-7)</th>
<th>Obs</th>
<th>Exp</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Never flying over five time zones:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cancers (140-205)</td>
<td>12</td>
<td>8.35</td>
<td>1.44</td>
<td>0.74 to 2.51</td>
</tr>
<tr>
<td>Malignant melanoma - skin (190)</td>
<td>1</td>
<td>0.11</td>
<td>9.09</td>
<td>0.12 to 50.58</td>
</tr>
<tr>
<td>Eye (192)</td>
<td>0</td>
<td>0.03</td>
<td>0.00</td>
<td>- to 122.27</td>
</tr>
<tr>
<td>Acute myeloid leukaemia (204)</td>
<td>0</td>
<td>0.08</td>
<td>0.00</td>
<td>- to 45.85</td>
</tr>
<tr>
<td><strong>Ever flying over five time zones:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cancers (140-205)</td>
<td>7</td>
<td>6.70</td>
<td>1.04</td>
<td>0.42 to 2.15</td>
</tr>
<tr>
<td>Malignant melanoma - skin (190)</td>
<td>4</td>
<td>0.16</td>
<td><strong>25.00</strong></td>
<td>6.73 to 64.00</td>
</tr>
<tr>
<td>Eye (192)</td>
<td>1</td>
<td>0.03</td>
<td>33.33</td>
<td>0.44 to 185.46</td>
</tr>
<tr>
<td>Acute myeloid leukaemia (204)</td>
<td>1</td>
<td>0.07</td>
<td>14.29</td>
<td>0.19 to 79.48</td>
</tr>
</tbody>
</table>

Occup Environ Med. 2000 Mar;57(3):175-9
Summary

- Genetics & hereditary features cannot be controlled:
  - inherited genes (you get what you’re born with)
  - random genetic mutations (fairly rare)

- Epigenetics & non-hereditary features can be controlled
  - environmental factors (air & water quality)
  - carcinogen exposure (smoking, UV light)
  - diet (high fat and/or high caloric intake)
How do we study cancer?

1. Tools
2. Targets
3. Technology
V. Research: Tools
V. Research: Tools

Cancer cells on a plate

Cancer cells in a mouse

Cancer cells injected
1. under the skin
2. at the site of origin (pancreas)

pancreatic cancer cells
V. Research: Tools

Engineering a Genetically Modified Mouse

1. candidate genes
   - ablate TSG
   - express oncogenes

2. gene switches for regulating expression

3. methods for building and inserting transgenes
V. Research: Tools

- A gene switch that can target specific cell types

**Single switch** – one room (cell type)  
**Multiple switch** – several rooms (cell types)
V. Research: Tools

Transgenesis
V. Research: Targets
V. Research: Targets

- The search for causative cell signals
  - determine which mutation/signal directly induces cancer a genetic change = contribution to cancer development

  - usually done in plated cells or rodents (the tools) must correlate to the human disease

  - probably multiple pathways – look for a circuit

  - can mutation or signaling pathway be blocked
V. Research: Technology
V. Research: Technology

- Engineer the means to block signals and circuits
  - drugs
    - effective (90% inhibition or better)
    - specific (only effect cells of interest)
  - radiotherapy
  - delivery mechanisms
    - best routes
    - nanotechnology
  - combined therapies
V. Research

Building tools and using them to evaluate targets and technologies for inhibition
V. Research: Precancer

- Prevention
  - Develop models with only precancer
  - Diet studies
  - Block certain pathways (inhibitors)
  - Tea evaluations
V. Research: Precancer

- Mouse Model Development

  Human precancer  Mouse precancer
V. Research: Precancer

- High fat diets
  - $\omega$-3, $\omega$-6, high tallow, Western-style diets

- Herbs
  - (Sutherlandia)

- Caerulein
  - (promotes inflammation)

- Carcinogens
  - (cadmium)
V. Research: Precancer

- Different types of PUFAs have varying affects
  - Compare omega-3 with omega-6 fatty acids

fish oil (omega-3)

corn oil (omega-6)
V. Research: Precancer

Frequency of precancerous lesions in EL-Kras Mice

Number of Precancerous Lesions

control  high corn oil  high fish oil
V. Research: Precancer

- Detection
  - Employ MRI to detect early cellular changes before and during precancer development
  - Proteomic profile of blood and secreted products
  - Vaccinate against known cancer markers
V. Research: Cancer

- Therapy
  - Develop models with pancreatic cancer
  - Chemo and/or Radiotherapy
  - Block certain pathways (inhibitors)
V. Research: Cancer

- Mouse Model Development

Human pancreatic cancer

Mouse pancreatic cancer
Liver Metastases in Pdx1-cre/LSL-Kras Mice

- Control
- GEM
- SHH
- I/G both

Percent Mice with Liver Mets

Science. 2009 Jun 12; 324(5933):1457-61
Drug Delivery using the same model

Optimal drug delivery (in green) in transplanted tumors (left panel)
Poor drug delivery in genetically engineered model (right panel)
Visualization by contrast ultrasonography.
VI. Prevention & Early Detection - Your Part

- What can you do?
  - Hereditary and random mutations = **early screening**
  - Epigenetics and non-hereditary = **minimize your risks**

- How can you minimize your risks?
  
  This is prevention
  1. Occupational hazards
  2. Diet: on and off “the clock”
  3. Other: personal stress and exposures
Vla. Prevention

- Occupational Risks
  - some exposure is unavoidable: part of the job
  - try to limit amount of exposure or reduce intensity
    - avoid repetitive high altitude/latitude routes over many years
    - keep track of annual radiation dose (mrems)
    - protection (sunblock/sunscreen, sunglasses, etc.)
  - keep stress levels in check
  - avoid or compensate for changes in light-dark cycles
  - encourage more research studies to be done
Vla. Prevention

- **Diet**
  - avoid foods that are:
    - rich in fat and/or fried in fat
    - overly processed (containing things like TRANS fats)
    - high in calories only
  - eat foods that are simply prepared and fresh
  - attempt to establish a healthy ratio of good fat (PUFA)
    - average w-6:w-3 ratio is about 30-40
    - a more healthy ratio is closer to 1
    - not just eating more fish – consider free-range meats
Vla. Prevention

- Non-occupational
  - limit sun exposure (every bit counts)
  - don’t smoke
  - avoid repetitive high levels of alcohol consumption
  - keep a modest traveling schedule to avoid further CD
  - maintain activities that you enjoy & reduce stress
Even with prudent work and lifestyle habits, cancer can develop.

Early detection is the best means of improved outcome:
- almost all cancers are treatable when detected early
- less invasion with no metastasis = very good prognosis
V1b. Early Detection

- How to detect cancer early
  - pay attention to your body
    1. differences in bodily functions
    2. pain or discomfort
  - regular/routine doctor visits
    1. colonoscopy for colon screening
    2. PSA test for prostate screening mammography for breast screening
  - best to start these screens in your late 40’s/early 50’s
Practical Application

What can you do with a diagnosis of cancer?
Practical Application

- Be informed
  - don’t hesitate to get a second opinion
  - read & study – learn as much as you can
  - be aware of various therapies and clinical trials
  - challenge your doctors
    remember, you’re not their only patient
  - seek out conventional and nutritional therapies

- Be positive
  - many, many people survive a cancer diagnosis

- Be spiritual - pray

Semin Oncol Nurs. 2005 Aug;21(3):159-63
Summary

- Cancer boils down to primarily two things:
  1. your genes – can’t control this but can know the risk
  2. the environment – can control most of this
     includes things like:
     - carcinogen exposure
     - diet and other lifestyle choices
Summary

What can be done to prevent this disease

1. my part = research
   The three T’s (tools, targets, technology)
   find new ways to prevent and fight cancer

2. your part = prevention
   reduce carcinogenic exposure
   balanced diet
   pay attention to your body
   routine check-ups (including the undesirables)
Acknowledgements

- ALPA
- Captain Bob Solik – ALPA Aeromedical Chairman
- Captain John Rosenberg
- Institutional Support & Mentoring over the years:
  - University of Wisconsin (Dr. Eric Sandgren)
  - Medical College of Wisconsin (Dr. Michael Demeure)
  - Northwestern University (Drs. Tom Adrian & Richard Bell)
    (Drs. Jill Pelling & Susan Crawford)

A Special Appreciation to all of you – for providing safe air travel