Biology of Ageing & Cancer

Hashim Missawi

FA Path., MD Geriatric Path. Germany,
BGS Membership, UK.
SAAARMM (Anti Aging) membership, Malaysia

Madinah Munawara M&C Hospital, KSA
Objectives

- To elucidate the incidence of cancer in old and elderly people in KSA & worldwide.
- To correlate this data with the molecular biology of tumor formation & ageing mechanisms.
- Planning for effective prevention & treatment of cancer in the elderly.
By mid-21st century, old people will outnumber young for the first time in history
Saudi Arabia is one of the countries showing a dramatic increase in the number of older people.
This study takes the most recent age specific incidence data from the Saudi National Cancer Registry in KSA as well as using data from several population-based cancer reports like those of the WHO & the International Association for Research on Cancer.

Scientific literature was reviewed to fit the available data with the biological changes in old age like increasing nuclear instability, apoptosis, telomere shortening and cell senescence.
Results

Marked increases in cancer incidence with ageing

Age-Specific Incidence Rates for Cancer among Saudis, 2009
Adults aged 50-74 carry the greatest burden of cancer. Over half (53%) of all cancers being diagnosed in this age group.

By the year 2030 more than 70% of new tumors will occur in individuals 65 years and older.
Different cancer types in different age groups

Cancer among Saudis 2009
Results

But a marked decrease with more ageing

Cancer among Saudis 2009
Cancer in Extremities of Age

Saudis 2009

Cancer is relatively rare in children. **Leukaemia** is the most common.
Hodgkin’s Dis.
CNS Tumors
Colo-rectal Cancer in KSA, 2002
Colo-rectal Cancer in KSA, 2009
Prostate Ca.

Prostate Cancer in KSA, 2002
Over a third (36%) of all cancers are diagnosed in the elderly. 75+

Compared to (53%) in the old 60-74.
The incidence and mortality for cancer level off around 85-90 years of age, followed by a plateau, or even a decline in the last decades of life.

All Cancers in KSA, 2009
Liver Ca

Fig. 3-5-1 Age-Specific Incidence Rate (AIR) for Liver Cancer in Saudi Arabia, 2002

Lung Ca

Fig. 3-8-1 Age-Specific Incidence Rate (AIR) for Lung Cancer in Saudi Arabia, 2002
Ovary

Uterus
Corpus Uteri Cancer in KSA, 2009
Breast Cancer in KSA, 2002
Breast Cancer in KSA, 2009
Fig. 2-1 Percentage Distribution of Cancer Incidence among Saudis by Sex according to Age Group, 2002
Outliving Our Cancers — Modeling Cancer Decreases at Old Age

![Graph showing age-specific incidence vs. age for different models and SEER data.]

- A-D power law
- MVK clonal expansion
- Beta model
- SEER (all sites M, F)

Figure 1. Age specific incidence vs. age curve shapes for the two major historical model types, compared to the Beta model and SEER data for combined male and female cancers.
Outliving Our Cancers — Modeling Cancer Decreases at Old Age

Figure 2a-f. Age specific incidence (per 100,000) vs. age for males and females. Beta distribution fits of SEER (Reis et al. 2000) data for non-gender-specific sites. Parameter values are listed for the Betal function form: \( f(x) = \frac{x^a}{B(a,b)} (1-x)^{b-1} \) with 100,000. The fit values are calculated as the fraction of the variance of the observed data which are accounted for by the Beta model with the listed parameter values.
Figure 3a-f. Age specific incidence (per 100,000) vs. age. Beta distribution fits of SEER (Reis et al. 2000) data for gender specific sites. Parameter values are listed for the Beta function form: \( f(t) = \frac{\alpha \beta}{(1 + \beta) \Gamma(\alpha + \beta)} t^{\alpha-1}(1-t)^{\beta-1} \), where \( t \) = age 15. The fit values are calculated as the fraction of the variance of the observed data, which are accounted for by the Beta model with the listed parameter values.
U.S. 1990 vital statistics:
Cancer deaths accounted for nearly 40% of all deaths occurring in adults between the ages of 50 and 69 years, only 4% of all deaths were due to cancer among centenarians.

Japanese study:
Centenarians had a 75% reduced prevalence of metastases and a 66% reduced rate of mortality caused by cancer compared with 90- to 94 year-olds.
3 categories of the elderly people:

- **Survivors** (age of onset before 80 years).
- **Delayers** (age of onset 80–99 years).
- **Escapers** (no diseases prior to age 100).
Table 3. Survivors, Delayers, and Escapers

<table>
<thead>
<tr>
<th>Morbidity Profile</th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>24</td>
<td>43</td>
<td>.00009</td>
</tr>
<tr>
<td>Delayers</td>
<td>44</td>
<td>42</td>
<td>.67</td>
</tr>
<tr>
<td>Escapers</td>
<td>32</td>
<td>15</td>
<td>.0003</td>
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</tbody>
</table>

Based on reports of the following disease states: heart disease, nonskin cancer, stroke, skin cancer, hypertension, Parkinson’s disease, COPD, diabetes, thyroid disorders, & osteoporosis

Based on reports of the above disease states, excluding thyroid disorders and osteoporosis

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<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>18</td>
<td>32</td>
<td>.009</td>
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<tr>
<td>Delayers</td>
<td>44</td>
<td>36</td>
<td>.15</td>
</tr>
<tr>
<td>Escapers</td>
<td>38</td>
<td>32</td>
<td>.30</td>
</tr>
</tbody>
</table>

Based on reports of the following disease states: heart disease, stroke, & nonskin cancer

<table>
<thead>
<tr>
<th>Morbidity Profile</th>
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<th>Female (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>13</td>
<td>17</td>
<td>.34</td>
</tr>
<tr>
<td>Delayers</td>
<td>36</td>
<td>34</td>
<td>.70</td>
</tr>
<tr>
<td>Escapers</td>
<td>51</td>
<td>49</td>
<td>.75</td>
</tr>
</tbody>
</table>

Notes: COPD = chronic obstructive pulmonary disease.
- **Tumor progression** is a complex process that depends on interactions between tumor and *host cells*.

- Most **premature aging** diseases are characterized by high **tumor susceptibility**. It is linked to the biological age.

- Elucidation of the **molecular** mechanism involved in **aging** is critical for advancing our understanding of **tumor formation**.
- Cells normally can divide only about 50 to 70 times, with telomeres getting progressively shorter until the cells become senescent, die or sustain genetic damage that can cause cancer.
- Cells from 75- to 90-year-old individuals had hallmarks of aging, including disorganized chromatin and increased levels of unrepaired DNA lesions. These simple observations were the first indication that changes in nuclear architecture are related to the aging process and tumorogenesis.
Five links between cancer biology and ageing

1- Cellular senescence.

2- Genomic instability links cancer and ageing.

3- The biology of the telomere.

4- The importance of autophagy in both cancer and ageing.

5- The central roles of mitochondrial metabolism and energetic-dependent signal transduction in both processes of ageing and cancer.
1- Cellular senescence

Hope from inside the tumor

- Cellular senescence is a state of permanent growth arrest that can be induced by a variety of stresses such as DNA-damage and aberrant mitogenic signaling in human primary cells.

- Abundant senescent cells within tumours.
1- Cellular senescence

- This intra-tumoral senescence is thought to be triggered mainly by oncogenic signals that can function in part by de-repressing the \( CDKN2a \) locus (aging biomarker).
- Activation of the DNA damage response (DDR) pathway is an oncogene-induced senescence.
- Rapid \textit{in vivo} clearance of tumour cells that undergo P53-triggered senescence
- In essence, cancer prevention might come at the expense of an accelerated decline in tissue regeneration and repair.
Standard chemotherapy and radiotherapy might function in part by inducing senescence within the tumour mass.

Local induced tumor senescence is a strategy that could protect us from cancer comes at the expense of accelerating ageing.

So, who is going to die first? Tumor or Host?
2- Genomic instability

- Genomic instability is a hallmark of cancer and aging.
- Age-dependent increase in chromosomal instability.
- Age-dependent accumulation of somatic mutations.
- Age-dependent germline mutations in the genes for p53. Normally regulated p53 could have a beneficial impact on longevity and protection against cancer by eliminating DNA damage (or DNA-damaged cells).
3- Telomeres

- Telomere length predicts the replicative capacity of human cells and the appearance of certain age-associated pathologies in humans.

- Increased telomerase activity in two independent Tert transgenic mouse models seemed to increase the susceptibility for tumor formation.

- In spite of their increased mortality due to cancer, these transgenic mice did show evidence of improved tissue regeneration as well as a slight increase in maximum life span.

- Telomere shortening represents a potent *in vivo* tumor suppressor mechanism.
3- Telomeres


- A link between long telomeres and an increased risk for colorectal cancer. American Association for Cancer Research special conference on Colorectal Cancer: Biology to Therapy, held in Philadelphia Oct. 27-30, 2010

- Forced elongation of telomeres promotes the differentiation of cancer cells, probably reducing malignancy. Japanese Foundation for Cancer Research in Tokyo, June 27, 2013
3- Telomeres

- While the shortening of telomeres is an unavoidable side effect of getting older, telomeres can also shorten as a result of sudden cell damage, including oxidative damage.

- Abnormally short telomeres have been found in osteoarthritis and some types of cancer, possibly because of the rapid cell division the cells are forced to undergo.

- Investigators have developed several telomerase-based therapeutic strategies, which are currently in clinical trials.
4- Autophagy and waste management

- Accumulation of damaged proteins and organelles is a hallmark of ageing and age-related diseases.

- From mice engineered to have lost one copy of the *Becn1* gene (impotent for regular autophagy), the haplo insufficient mice developed tumors, indicating that autophagy might act as an important *in vivo* tumor suppressor.
Mutations that prolong lifespan are often intimately connected with the ability of the organism to withstand stress, particularly oxidative and metabolic stress.

This same stress resistance might also be important to a rapidly growing tumor cell, where the supply and availability of nutrients and oxygen are often precarious.

This strategic metabolic overlap has been made more concrete by observations of specific genes that link together the triad of lifespan, cancer and energetics. One such gene is *Trp53*, which encodes p53.
Aging Markers Tumor Markers

Delayed ageing through damage protection by the Arf/p53 pathway.

Loss of the INK4a/ARF/INK4b locus on chromosome 9p21 is among the most frequent cytogenetic events in human cancer.

Recent data also suggest that expression of p16INK4a induces an age-dependent decrease in the proliferative capacity of certain tissue-specific stem cells and unipotent progenitors.
The complexity of ageing and the biology of cancer do not lend themselves to easy generalizations.

cancer and ageing seem to share common, rather than antagonistic, aetiologies.

The steep age-related increase in cancer incidence suggest that cancer is just one of a host of age-related pathologies.
Cancer and ageing can be viewed as pure stem cell diseases, with cancer representing the effect of additional growth promoting mutations within a given stem cell and ageing representing the natural exhaustion and depletion of the stem and progenitor pool.

A key feature of HG-progeria is the absence of tumors. HGPS could be a useful model system for delineating the molecular links between aging and tumor formation.
Conclusion

- KSA and international aging and cancer profiles are highlighted.

- **Aging** is a major cancer risk factor. It is estimated that by the year 2030 more than 70% of new tumors will occur in individuals 65 years and older.

- Elucidation of the molecular mechanism involved in aging & premature aging diseases is critical for advancing our understanding of tumor formation.
Based on these results, it is proposed that telomeres also modulate the behavior of cells by controlling gene expression, and may ultimately lead to new types of treatments for cancer.

Information is needed on how age-related health problems affect cancer prevention, detection, prognosis, and treatment.
Cancer and old age associated diseases are 3rd world major health problems
Peaceful greetings from Medina