Scientific Evidence for the Role of Nutrition in Prostate Cancer.

Jeff Holly
IGFs & Metabolic Endocrinology Group.
Southmead Hospital. University of Bristol
UK

- Evidence
- Myths

Bristol Prostate Cancer Research Network
Prostate cancer remains the most commonly diagnosed malignancy among men in the United States. It accounted for one quarter of the 745,180 estimated new cancers diagnosed in men in 2008, according to the American Cancer Society. The top five cancers in American men are shown here.

- Prostate: 186,320 cases
- Lung & bronchus: 114,690 cases
- Colon & rectum: 77,250 cases
- Urinary bladder: 51,230 cases
- Non-Hodgkin lymphoma: 35,450 cases
FIGURE 6 Death Rates* for Cancer and Heart Disease for Ages Younger than 85 and 85 and Older, 1975 to 2004

Why do we get cancer?
• Cancers are initiated by gene mutations.

How often do gene mutations occur?
Frequent clones of p53-mutated keratinocytes in normal human skin

(sunlight/ultraviolet/carcinogenesis/tumor promotion/clonal expansion)

ALAN S. JONASON*, SUBRAHMANYAM KUNALA*, GARY J. PRICE†, RICHARD J. RESTIFO‡, HENRY M. SPINELLI‡, JOHN A. PERSING‡, DAVID J. LEFFE‡, ROBERT E. TARONE‡, and DOUGLAS E. BRASH***†††

Departments of *Therapeutic Radiology, †Dermatology, and ‡Genetics, and †Section of Plastic Surgery, Department of Surgery, and **Yale Comprehensive Cancer Center, Yale School of Medicine, New Haven, CT 06510; †Connecticut Center for Plastic Surgery, New Haven, CT 06511; and ‡Biostatistics Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20205

ABSTRACT The multiple genetic hit model of cancer predicts that normal individuals should have stable populations of cancer-prone, but noncancerous, mutant cells awaiting further genetic hits. We report that whole-mount preparations of human skin contain clonal patches of p53-mutated keratinocytes, arising from the dermal–epidermal junction and from hair follicles. These clones, 60–3000 cells in size, are present at frequencies exceeding 40 cells per cm² and together involve as much as 4% of the epidermis.
• Gene mutations are present in large numbers of cells in normal tissues.
The Role of Prevalence in the Diagnosis of Prostate Cancer

Nicolas B. DeLongchamps, MD, Amar Singh, MD, and Gabriel P. Haas, MD

Autopsy Prevalence Rates of Prostate Cancer Worldwide (%)

% of men with abnormal growths in their prostate gland

- USA
- Spain
- Japan
- Greece
- Hungary

Age

21-30 31-40 41-50 51-60 61-70 71-80
• Gene mutations are present in large numbers (millions) of cells in normal tissues.

• Latent occult cancers (abnormal growths) occur normally, with increasing prevalence as we age. If we live to old age we will all develop latent cancers.

• However, relatively few people develop clinical cancers.
Prostate cancer epidemiology

Henrik Grönberg

Lancet 361; 2003, 859-864
Cancer Rates in Migrants Converge to that of Locals

% Cumulative Rate by age 75

- Japanese Osaka 70-71
- Japanese Osaka 88-92
- Japanese Hawaii 88-92
- Hawaii Caucasians 68-72
- Hawaii Caucasians 88-92

Prostate
ENVIRONMENTAL AND HERITABLE FACTORS IN THE CAUSATION OF CANCER

Analyses of Cohorts of Twins from Sweden, Denmark, and Finland

Paul Lichtenstein, Ph.D., Nils V. Holm, M.D., Ph.D., Pa K. Verkasalo, M.D., Ph.D., Anastasia Iliadou, M.Sc., Jannik Kaprio, M.D., Ph.D., Markus Koskenvuo, M.D., Ph.D., Eero Pukkala, Ph.D., Axel Skytthe, M.Sc., and Kari Hemminki, M.D., Ph.D.

44,788 pairs of twins listed in the Swedish, Danish, and Finnish twin registries

![Bar chart showing proportion of variance for Breast, Colorectal, and Prostate cancers. Heritable factors and Environmental factors are compared. The chart indicates that Heritable factors contribute significantly more to Breast and Prostate cancers, while Environmental factors contribute more to Colorectal cancer.]
Relative Risk Of Cancer for Offspring

Biologic Parent

Adopted Parent

Parent Died of Cancer Before age 50.

Genetic and environmental influences on premature death in adult adoptees

TI Sorensen, GG Nielsen, PK Andersen, and TW Teasdale

Volume 318:727-732 March 24, 1988 Number 12
• Do environmental exposures affect genetic predisposition?
Breast and Ovarian Cancer Risks Due to Inherited Mutations in BRCA1 and BRCA2

Mary-Claire King,1* Joan H. Marks,2 Jessica R. Mandell2* for
The New York Breast Cancer Study Group3

A

Risk of breast cancer in BRCA1/2 carriers (%)

Age

Born after 1940

Born before 1940

Laufey Tryggvadóttir, Helgi Sigvaldason, Guðrúður H. Olafsdóttir, Jon G. Jonason, Thorvaldur Jonason, Hinna Thelínus, Jórunn E. Eskifjördi

Journal of the National Cancer Institute, Vol. 98, No. 2, January 18, 2006 116–22

Cumulative incidence of breast cancer before age 70 years by birth period

- General Population
- BRCA2 mutation carriers
Epidemiology

Diet, lifestyle and BRCA-related breast cancer risk among French-Canadians

A. Nkondjoek, A. Robidoux, Y. Paredes, S.A. Narod, P. Ghadirian

Total energy intake

<table>
<thead>
<tr>
<th>Kcal/d</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1724</td>
<td>1</td>
</tr>
<tr>
<td>1724-2339</td>
<td>1.5</td>
</tr>
<tr>
<td>&gt;2339</td>
<td>3</td>
</tr>
</tbody>
</table>

Weight gain since age 18

<table>
<thead>
<tr>
<th>lbs</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12</td>
<td>1</td>
</tr>
<tr>
<td>12 to 35</td>
<td>3.5</td>
</tr>
<tr>
<td>&gt;35</td>
<td>5</td>
</tr>
</tbody>
</table>
IGF-I

Childhood Nutrition

Growth

Cancer Risk
Serum IGF-I levels in Boys aged 7 according to milk consumption.

P = 0.012
ORIGINAL ARTICLE

Childhood diet and insulin-like growth factors in adulthood: 65-year follow-up of the Boyd Orr Cohort

RM Martin¹, JMP Holly², N Middleton¹, G Davey Smith¹ and D Garnell¹

1,167 subjects investigated prospectively (aged 2-8 years).

60 year follow-up.

12 deaths from sex-hormone dependent cancer (breast, ovarian & prostate).

Leg length measured (adjusted for sex, age & trunk length).

Leg Length and hormone-dependent cancers:

Hazard Ratio 2.29 (p=0.03)

associated with one standard deviation score increase in leg length

-approximately 4mm.
IGFs and prostate cancer risk: a collaborative analysis of twelve prospective studies.

The Endogenous Hormones and Prostate Cancer Collaborative Group.

3350 Cases, 4550 Controls.

Risk of prostate cancer (red) per SD increase in IGF-I* compared with risks of IHD (blue) per SD increase in IGF-I & classic risk factors**

*data from Renehan et al. Lancet 2004;363: 1346–53
**data from Juul A. Circulation 2002;106:939-944
Serum IGF-I levels according to milk consumption.

![Bar chart showing serum IGF-I levels according to milk consumption](chart.png)

- **Milk consumption** (Pints per day):
  - <0.5: N=95
  - 0.5-0.75: N=173
  - 1+: N=74

- **IGF-I ng/ml**:
  - <0.5
  - 0.5-0.75
  - 1+

- **P=0.004**

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**Short Communication**

Serum IGF-I levels in Men aged 50-70 according to tomatoes and ketchup consumption.

<table>
<thead>
<tr>
<th>IGF-I (ng/ml)</th>
<th>Tomatoes Consumption (times per week)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>N=233</td>
<td>P=0.19</td>
</tr>
<tr>
<td>1 to 4</td>
<td>N=100</td>
<td></td>
</tr>
<tr>
<td>&gt;5</td>
<td>N=10</td>
<td>P=0.10</td>
</tr>
</tbody>
</table>

Ketchup consumption times per week
• Nutrition affects hormones which may determine whether prostate cancers progress.

• Is there anything that we can do about it?
Effect of Hyperglycaemia on the Response of Prostate Cancer Cells to Docetaxel

% Dead Cells

Glucose concentration (mM)

Without Docetaxel

With Docetaxel

0 5 5.625 6.25 7.5 10 15 25

5 5.625 6.25 7.5 10 15 25

% Dead Cells

5 5.625 6.25 7.5 10 15 25

0 2 4 6 8 10 12 14 16 18 20

Without Docetaxel

With Docetaxel
Metformin enhances docetaxel effectiveness and negates the effect of hyperglycaemia
Cancer Research

Physical Activity after Diagnosis and Risk of Prostate Cancer Progression: Data from the Cancer of the Prostate Strategic Urologic Research Endeavor


Cancer Res Published OnlineFirst May 24, 2011.
Prostate Cancer Mortality.
‘unable to move,
Kev realises that he has buried the wrong nuts’
Relative Survival* (%) during Three Time Periods by Cancer Site

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>50</td>
<td>52</td>
<td>63</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>75</td>
<td>78</td>
<td>87</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>50</td>
<td>57</td>
<td>62</td>
</tr>
<tr>
<td>Leukemia</td>
<td>34</td>
<td>41</td>
<td>46</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>12</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Melanoma</td>
<td>80</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>47</td>
<td>54</td>
<td>56</td>
</tr>
<tr>
<td>Ovary</td>
<td>37</td>
<td>41</td>
<td>53</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Prostate</td>
<td>67</td>
<td>75</td>
<td>98</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>73</td>
<td>78</td>
<td>82</td>
</tr>
</tbody>
</table>

*5-year relative survival rates based on follow up of patients through 2000.
## Number of additional men diagnosed and treated for prostate cancer since the start of prostate-specific antigen screening*

<table>
<thead>
<tr>
<th>Age group, y</th>
<th>No. of additional men diagnosed</th>
<th>No. of additional men treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Surgery</td>
</tr>
<tr>
<td>20–49</td>
<td>50 500</td>
<td>33 800</td>
</tr>
<tr>
<td>50–59</td>
<td>325 100</td>
<td>194 400</td>
</tr>
<tr>
<td>60–69</td>
<td>610 100</td>
<td>273 900</td>
</tr>
<tr>
<td>70–79</td>
<td>386 600</td>
<td>69 700</td>
</tr>
<tr>
<td>80</td>
<td>−66 700</td>
<td>−700</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1 305 600</strong></td>
<td><strong>571 000</strong></td>
</tr>
</tbody>
</table>

* In the years following 1986 through 2005. Numbers may not add precisely because of rounding.

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Prostate Cancer Diagnosis and Treatment After the Introduction of Prostate-Specific Antigen Screening: 1986–2005.

Fig 3 Kaplan-Meier curves of prostate cancer specific survival for men diagnosed with prostate cancer in control group (n=292) and screened group (n=85).

Men at risk:

<table>
<thead>
<tr>
<th></th>
<th>Screened</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>81</td>
<td>275</td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>216</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>135</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>72</td>
</tr>
</tbody>
</table>

Sandblom G et al. BMJ 2011;342:bmj.d1539
Prostate cancer–specific mortality for patients who were treated with surveillance, radiation therapy, or radical prostatectomy in the National Prostate Cancer Register (NPCR) of Sweden Follow-up Study.A) Combination of low- and intermediate-risk patients.


© The Author 2010. Published by Oxford University Press.
A new understanding of cancer development is emerging.

New opportunities for intervention & prevention strategies.

You can also help yourself by a healthy lifestyle:-

- Reduce the animal protein in your diet, especially dairy products.
- Eat more fruit and vegetables.
- Exercise regularly.
Change in the US Death Rates* by Cause, 1950 & 2001

<table>
<thead>
<tr>
<th>Cause</th>
<th>1950 Rate Per 100,000</th>
<th>2001 Rate Per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Diseases</td>
<td>586.8</td>
<td>245.8</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>180.7</td>
<td>57.5</td>
</tr>
<tr>
<td>Pneumonia/Influenza</td>
<td>48.1</td>
<td>21.8</td>
</tr>
<tr>
<td>Cancer</td>
<td>193.9</td>
<td>194.4</td>
</tr>
</tbody>
</table>

* Age-adjusted to 2000 US standard population.

Sources:
1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf
Prostate cancer incidence and mortality rates in U.S. men (white) and in U.K. men (all races).
Fig. 1. Prostate cancer mortality versus sugar consumption in 71 countries.
Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D.,
Teuvo L.J. Tammiela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D.,
Maciej Kwatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D.,
Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D.,
Antonio Berenguer, M.D., Liisa Määtänen, Ph.D., Chris H. Bangma, M.D.,
Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D.,
Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D.,
Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators®


This means that 1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent one death from prostate cancer.
Fig 4 Cumulative rates of prostate cancer specific mortality.

Sandblom G et al. BMJ 2011;342:bmj.d1539
Prostate cancer incidence in the world.


USA, SEER 112.3
Australia, New South Wales 90.1
Canada 80.2
Sweden 63.0
Colombia (1992–1996) 42.2
UK, England 39.6
Czuch Republic 32.0
Denmark 29.9
Poland, Wasaw City 22.2
Singapore 13.9
Japan, Osaka 9.9
China, Hong Kong 8.6
India 7.4

Note: Rates are per 100,000 standardized to the World population. Sites are ranked in decreasing order.
Source: Surveillance and Risk Assessment Division, CCDPC, Health Canada

### 2004 Estimated US Cancer Cases*

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Oral Cavity</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>All Other Sites</td>
<td>18%</td>
<td></td>
</tr>
</tbody>
</table>

- **Men:** 699,560 cases
- **Women:** 668,470 cases

- **Prostate:** 33%
- **Lung & bronchus:** 13%
- **Colon & rectum:** 11%
- **Urinary bladder:** 6%
- **Melanoma of skin:** 4%
- **Non-Hodgkin lymphoma:** 4%
- **Kidney:** 3%
- **Oral Cavity:** 3%
- **Leukemia:** 3%
- **Pancreas:** 2%
- **All Other Sites:** 18%

- **Women:**
  - **Breast:** 32%
  - **Lung & bronchus:** 12%
  - **Colon & rectum:** 11%
  - **Uterine corpus:** 6%
  - **Ovary:** 4%
  - **Non-Hodgkin lymphoma:** 4%
  - **Melanoma of skin:** 4%
  - **Kidney:** 3%
  - **Oral Cavity:** 3%
  - **Leukemia:** 3%
  - **Pancreas:** 2%
  - **Urinary bladder:** 2%
  - **All Other Sites:** 20%

**Childhood Nutrition and Cancer**

*(S Frankel et al. BMJ 316: 1998; 499.)*

  - 3,834 subjects investigated prospectively (aged <16 years).
  - 57-59 year follow-up.
  - 203 deaths from cancer.
  - Dietary intake assessed by weight and composition of food over 1 week.

- Dietary energy intake:
  - **Hazard Ratio 1.15 (p=0.001)**
    - per 1 MJ/day (239 kcal) adjusted for social variables.
IGF-I concentration

Cardiovascular Disease
Type 2 Diabetes
Osteoporosis
Sarcopenia
Cognitive Decline

Cancer
IGF-I and mammographic density in four geographic locations: A pooled analysis

Gertraud Maskarinec\textsuperscript{18}, Yumie Takata\textsuperscript{2}, Zhao Chen\textsuperscript{3}, Inger Torhild Gram\textsuperscript{4}, Chisato Nagata\textsuperscript{5}, Ian Pagano\textsuperscript{1}, Kentaro Hayashi\textsuperscript{6}, Leslie Arendell\textsuperscript{4}, Guri Skeie\textsuperscript{4}, Sabina Rinaldi\textsuperscript{7} and Rudolph Kaaks\textsuperscript{8}

From Table II. Mean serum IGF-I by location and ethnicity.
Sugar rush. PET scans reveal tumors (arrows) by highlighting areas of increased glucose uptake.
Risk of prostate cancer mortality according to physical activity.

Quintiles Physical Activity

Relative risk
Prostate Cancer Specific mortality
Why prostate cancer?

Estimated age-standardised mortality rate per 100,000
Prostate, all ages
Regression models for age prevalence of colorectal adenomas (A) and hyperplastic polyps (B) in the general population.

△, Autopsy studies;
○, screening colonoscopy studies.

Risk of prostate cancer (red) per SD increase in IGF-I* compared with risks of IHD (blue) per SD increase in IGF-I & classic risk factors**

*data from Renehan et al. Lancet 2004;363: 1346–53
**data from Juul A. Circulation 2002;106:939-944
Cancer Rates in Migrants Converge to that of Locals


% Cumulative Rate by age 75