Sedentary Behaviors and Cancer: Possible Risks and Biological Mechanisms

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Washington, DC
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Overview

• AICR Orientation
• Descriptive epidemiology
• Sedentary behavior and cancer risk
• Proposed biological mechanisms
  – Behavioral mechanisms
  – Study design
• Summary / conclusions
**Physical Activity Recommendation**
**WCRF/AICR 2007**

“Be physically active as a part of everyday life”

**Public Health Goal**
- The proportion of the population that is sedentary* to be halved every 10 years
- Average physical activity levels (PALs) to be above 1.6

* Sedentary = low physical activity level (PAL < 1.4)

**Personal Recommendations**
- Be moderately physically active,…~brisk walk, 30 min/d
- As fitness improves, aim for…~2 x volume, mod. or vigorous
- Limit sedentary habits such as watching television
Time spent in sedentary behavior (%), by sex and age - US 2003-2004

Matthews et. al. AJE, 2008

National average = 54.9%, or 7.7 hrs/d
15.4 hrs waking → 8.5 hrs/d sedentary

National Cancer Institute
Hours/day reported* in active and sedentary behaviors during waking hours

Adults (hrs/d, n=102)

- Sedentary: 3.40
- Light: 1.52
- Moderate: 0.20
- Vigorous: 9.92 (65.6%)

Adolescents (hrs/d, n=117)

- Sedentary: 2.29
- Light: 1.47
- Moderate: 0.62
- Vigorous: 9.76 (68.7%)

* Average from up to 3 24PARs over 7-10 days

National Cancer Institute
Sedentary behavior positively associated with:
• Colorectal
• Endometrial
• Ovarian
• Prostate
• Cancer mortality
Physical activity and colon cancer


Physical Activity Guidelines for Americans (2008)
JOB ACTIVITY AND COLON CANCER RISK

DAVID H. GARABRANT,¹ JOHN M. PETERS,¹ THOMAS M. MACK² AND LESLIE BERNSTEIN¹


The authors studied 2,950 population-based colon cancer cases in males in Los Angeles County, California, that were diagnosed between 1972 and 1981. To determine if colon cancer risk is reduced by physical activity on the job in males aged 20–64 years, the authors first rated each occupation by judging the activity level as high, moderate, or sedentary. Men with sedentary jobs had a colon cancer risk at least 1.6 times that of men whose jobs required a high level of activity. Risk increased in a stepwise manner as activity level decreased. This gradient was consistently seen within each socioeconomic stratum, among whites, blacks, immigrant and native Hispanics, and for each subsection of the colon from the hepatic flexure to the sigmoid. The protective effect of physical activity was very strong in the descending colon and diminished in a gradient both proximally and distally. There was no such relationship between physical activity and risk for rectal cancer. Physical activity may play a major, previously unrecognized role in colon cancer etiology. Such a role is consistent with the known pattern of colon cancer occurrence and with our understanding of colon physiology and colon cancer pathogenesis. In addition to the implications for prevention, understanding the effects of physical activity on colon cancer risk may allow future studies to evaluate more accurately the role played by diet.
Odds ratios for television and occupational activity on risk of colorectal cancer (360 cases/controls; Poland)

Television viewing
- 2+ hours/d: 0.79
- 1.14-1.99 hours/d: 0.47
- < 1.14 hours/d: 1.00

Occupational activity and television (TV) viewing
- Low = sit/stand
- Moderate: 0.49
- High: 0.23
- 2+ hours/d: 1.00
- 1.14-1.99 hours/d: 0.97
- < 1.14 hours/d: 0.67
Sedentary Behaviors and Colon Cancer Risk – NIH-AARP Diet and Health Study

Howard et al. Cancer Causes Control 19; 939, 2008

Men

<table>
<thead>
<tr>
<th>Hrs/d</th>
<th>&lt; 3</th>
<th>3-4</th>
<th>5-6</th>
<th>7-8</th>
<th>9+</th>
</tr>
</thead>
<tbody>
<tr>
<td>TV</td>
<td>1.00</td>
<td>1.16</td>
<td>1.26</td>
<td>1.19</td>
<td>1.61</td>
</tr>
<tr>
<td>OSS</td>
<td>1.00</td>
<td>1.21</td>
<td>1.23</td>
<td>1.24</td>
<td>1.24</td>
</tr>
</tbody>
</table>

\[ P_{\text{trend}} < 0.01 \]

Women

<table>
<thead>
<tr>
<th>Hrs/d</th>
<th>&lt; 3</th>
<th>3-4</th>
<th>5-6</th>
<th>7-8</th>
<th>9+</th>
</tr>
</thead>
<tbody>
<tr>
<td>TV</td>
<td>1.00</td>
<td>0.94</td>
<td>1.03</td>
<td>1.04</td>
<td>1.24</td>
</tr>
<tr>
<td>OSS</td>
<td>1.00</td>
<td>1.00</td>
<td>1.04</td>
<td>1.04</td>
<td>0.96</td>
</tr>
</tbody>
</table>

\[ P_{\text{trend}} = 0.17 \]

Adjusted Hazard Ratio

*Age, education, race, family history CRC, smoking, alcohol, energy intake, meat, calcium, whole grains, Fruits and vegetables, light-moderate-vigorous physical activity
Minireview
Physical activity, sedentary behaviours, and the prevention of endometrial cancer

SC Moore*,†, GL Gierach†, A Schatzkin† and CE Matthews†
†Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, Bethesda, MD 20892, USA

Occupational activity – prospective studies

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moradi 1998</td>
<td>0.76</td>
<td>0.67, 0.86</td>
</tr>
<tr>
<td>Weiderpass 2001</td>
<td>0.77</td>
<td>0.66, 0.90</td>
</tr>
<tr>
<td>Furberg 2003</td>
<td>0.49</td>
<td>0.26, 0.91</td>
</tr>
<tr>
<td>Friberg 2006</td>
<td>0.97</td>
<td>0.72, 1.31</td>
</tr>
<tr>
<td>Friedenreich 2007</td>
<td>0.89</td>
<td>0.63, 1.26</td>
</tr>
<tr>
<td>Combined</td>
<td>0.75</td>
<td>0.68, 0.83</td>
</tr>
</tbody>
</table>

The use of occupational activity, defined as working, housework, and gardening, may be protective against endometrial cancer. Physical activity may counteract the sedentary lifestyle associated with increased cancer risk. Taken together, these findings support the importance of physical activity in the prevention of endometrial cancer.
Sedentary Behaviors and Endometrial Cancer risk – NIH-AARP Diet and Health Study

Gierach et al.
Int J Ca 124; 2139, 2009

Moore et. al.
BJC 103; 933, 2010

P$_{trend}$ < 0.01

Adjusted Hazard Ratio

Television

Overall Sitting

National Cancer Institute
Sedentary Behaviors and Endometrial Cancer Risk

**Patel (2008) - prospective**

- Sitting - leisure
  - < 3: 1.00
  - 3-5: 1.13
  - 6+: 1.4
  - \( P_{\text{trend}} = 0.05 \)

**Friberg (2006) - prospective**

- Television - leisure
  - < 5: 1.00
  - 5+: 1.8

*Adjusted for physical activity indices*
Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects

C M Friedenreich,1 A E Cust2

ABSTRACT
Objective: To review (1) the epidemiological literature on physical activity and the risk of breast cancer, examining the effect of the different parameters of activity and effect modification within different population subgroups; and (2) the biological mechanisms whereby physical activity may influence the risk of breast cancer.

Methods: A review of all published literature to September 2007 was conducted using online databases; 34 case-control and 28 cohort studies were included. The impact of the different parameters of physical activity on the association between activity and the risk of breast cancer was examined by considering the type of activity performed, the timing of activity over the life course and the intensity of activity. Effect modification of this association by menopausal status, body mass index (BMI), racial group, family history of breast cancer, hormone receptor status, energy intake and parity were also considered.

Results: Evidence for a risk reduction associated with increased physical activity was found in 47 (76%) of 62 studies included in this review with an average risk decrease of 25–30%. A dose-response effect existed in 29 of 33 studies. Stronger decreases in risk were observed for recreational activity, lifetime or later life activity, vigorous activity, among postmenopausal women, women with normal BMI, non-white racial groups, those with hormone receptor negative tumours, women without a family history of breast cancer and parous women.

Conclusions: The effect of physical activity on the risk of breast cancer is stronger in specific population subgroups and for certain parameters of activity that need to be further explored in future intervention trials.

Figure 3 Studies of occupational physical activity and breast cancer risk.
# Sedentary behaviors and breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Risk estimate</th>
<th>$P_{\text{trend}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dirx (2001)</td>
<td>Prospective</td>
<td>0.83 (0.6-1.1)</td>
<td>0.54</td>
</tr>
<tr>
<td>Occupational sitting (&lt; 2 h/d (ref) vs. 6-8 h/d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matthew (2009)</td>
<td>Case-control (post-menop)</td>
<td>0.83 (0.5-1.4)</td>
<td>0.33</td>
</tr>
<tr>
<td>Television – weekdays (0-1 (ref) vs. 3+ h/d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Television – weekend (0-1 (ref) vs. 3+ h/d)</td>
<td>1.01 (0.6-1.6)</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>George (2010)</td>
<td>Prospective</td>
<td>1.17 (0.9-1.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>Television watching (&lt; 3 (ref) vs. 9+ h/d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall sitting (&lt; 3 (ref) vs. 9+ h/d)</td>
<td>1.12 (0.9-1.5)</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>
Full Paper

Physical activity and breast cancer risk in Chinese women

A Pronk¹, B-T Ji¹, X-O Shu², W-H Chow¹, S Xue¹, G Yang², H-L Li³, N Rothman¹, Y-T Gao³, W Zheng² and CE Matthews⁸,¹,²

¹Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, EFS 8100, MSC 7240, Bethesda, MD 20892, USA; ²Department of Medicine, Vanderbilt Epidemiology Center, Institute for Medicine and Public Health, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN 37203, USA; ³Department of Epidemiology, Shanghai Cancer Institute, Shanghai, People’s Republic of China

BACKGROUND: The influence of different types and intensities of physical activity on risk for breast cancer is unclear.

METHODS: In a prospective cohort of 73,049 Chinese women (40–70 years), who had worked outside the home, we studied breast cancer risk in relation to specific types of self-reported and work history-related physical activity, including adolescent and adult exercise and household activity and walking and cycling for transportation. Occupational sitting time and physical activity energy expenditure were assigned based on lifetime occupational histories.

RESULTS: In all, 717 incident breast cancer cases were diagnosed. Breast cancer risk was lower for women in the lowest quartile of average occupational sitting time and in the highest quartile of average occupational energy expenditure (adjusted hazard ratio (HR): 0.81 and 0.73, respectively, P≤0.05). Adult exercise at or above the recommended level (8 metabolic equivalent (MET) h per week per year) was associated with lower risk (adjusted HR: 0.73, P<0.05) in post-menopausal women. Analysis of joint effects showed that having both an active job and exercise participation did not confer an additional benefit. Other common daily activities were not associated with lower risk.

INTERPRETATION: These findings suggest that both exercise and occupational activity are associated with lower breast cancer risk, which supports current health promotion campaigns promoting exercise.

Sedentary Behaviors and Breast Cancer Risk – Shanghai Women’s Health Study

Occupational sitting

<table>
<thead>
<tr>
<th>Avg. sitting (hr/d)</th>
<th>Yrs Jobs &lt; 2 h/d sitting</th>
</tr>
</thead>
<tbody>
<tr>
<td>4+</td>
<td>Ptrend = 0.04</td>
</tr>
<tr>
<td>3.7-3.9</td>
<td>0.82</td>
</tr>
<tr>
<td>1.2-3.6</td>
<td>0.81</td>
</tr>
<tr>
<td>&lt;1.2</td>
<td>Ptrend = 0.02</td>
</tr>
<tr>
<td>0</td>
<td>0.87</td>
</tr>
<tr>
<td>1-10</td>
<td>0.83</td>
</tr>
<tr>
<td>11-24</td>
<td>0.74</td>
</tr>
<tr>
<td>25+</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted Hazard Ratio
Sedentary Behavior and Other Sites

**Ovarian**

*Patel (2006) – prospective*

<table>
<thead>
<tr>
<th>Activity</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting – leisure</td>
<td>1.51</td>
<td>(1.1-2.2)</td>
</tr>
</tbody>
</table>

*Zhang (2004) – case/control*

<table>
<thead>
<tr>
<th>Activity</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work sitting</td>
<td>1.96</td>
<td>(1.2-3.2)</td>
</tr>
<tr>
<td>TV sitting</td>
<td>3.39</td>
<td>(1.0-11.5)</td>
</tr>
<tr>
<td>Other sitting</td>
<td>0.83</td>
<td>(0.4-1.5)</td>
</tr>
<tr>
<td>Total sitting</td>
<td>1.77</td>
<td>(1.0-3.1)</td>
</tr>
</tbody>
</table>

**Renal/kidney**

*George (2011) - prospective*

<table>
<thead>
<tr>
<th>Activity</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Television watching</td>
<td>0.96</td>
<td>(0.7-1.4)</td>
</tr>
<tr>
<td>Overall sitting</td>
<td>1.11</td>
<td>(0.9-1.4)</td>
</tr>
<tr>
<td>Studies (⁺)</td>
<td>Result</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Men, women?</td>
<td></td>
</tr>
<tr>
<td>Endometrial</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>Null</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Null</td>
<td></td>
</tr>
</tbody>
</table>
Biological mechanisms

- Behavioral mechanisms
- Proposed biological mechanisms
Behavioral mechanisms

• Many more hours per day of sedentary behavior vs. modest amount of exercise each week (among exercisers)

• Displacement hypothesis
  – Time sedentary displaces time in active behaviors (light, moderate), and results in less overall physical activity
Activity Intensity and PA Level (PAL)

Vigorous activity
Inactive/sedentary
Light to moderate activity

Westerterp Nature 410: 539, 2001
Levine et. al. Science 307: 584, 2005

Fig. 1. (A) Time allocation for different postures for 10 obese and 10 lean sedentary subjects. Data are shown as mean ± SEM. Significant differences.
Figure 1 | Hypothesized mechanisms linking physical activity to cancer risk or prognosis. Physical activity might work through reducing the amount of adipose tissue, which lowers production of sex hormones, insulin, leptin and inflammatory markers, thereby decreasing the exposure to these potentially carcinogenic hormones and peptides and reducing cancer risk.
Study Designs Employed

**Intervention/experimental studies**
- Detraining (athletes → bed rest/stop training)
- De-activation (normal people → bed/chair rest)
- RE-activation (normal people → stand & move)

**Observational studies**
- Space travel/microgravity, Spinal cord injury
- Cross-sectional
- Prospective

**Age:** 27.1 yrs  
**BMI:** 22.9 kg/m²

**Over 3 weeks**  
OGTT: ↑ insulin

**Substudy 1**  
(n=8)  

**Age:** 23.8 yrs  
**BMI:** 22.1 kg/m²

**Over 2 weeks**  
OGTT: ↑ insulin, C-peptide  
OFTT: ↑ triglycerides  
Intra-abdominal fat ↑  
Fat-free mass ↓  
BMI ↓

Squares indicate mean values.
Design: Five days of bed rest (< 30 min/d upright/active)

Adverse effects:
• insulin resistance
• triglycerides, total cholesterol
• micro-vascular function
• systolic blood pressure

No effect:
• inflammatory markers (CRP)
Objective—To examine the proportion of objectively measured time spent sedentary and whether this associates with insulin resistance independent of moderate- and vigorous-intensity physical activity and other relevant confounders.

RESEARCH DESIGN AND METHODS—A population-based study (Medical Research Council's National Survey of Health and Development) of 5,365 middle-aged adults (166 men; 210 women) was followed up. Physical activity and sedentary time were objectively measured by individually calibrated rate monitors at baseline and follow-up. Sedentary time was defined as time spent sitting or standing at a heart rate below 100 beats per minute. Resting heart rate was calculated as the heart rate obtained on an individually predetermined time. The proportion of total self-report sedentary time was expressed as a percentage of total daily hours over 4 days. The percentage of resting heart rate represented the metabolic equivalent of task (MET) used as a surrogate measure of insulin resistance.

RESULTS—Time spent sedentary was positively associated with log-transformed fasting plasma insulin (β = 0.003, 95% CI 0.0006–0.006, P < 0.0001), adjustment for baseline age, sex, fat mass, fasting glycemia, and follow-up time. After further adjustment for body mass index, the association was somewhat strengthened (β = 0.006, P = 0.009).

CONCLUSIONS—Time spent sedentary was independently associated with fasting insulin and the importance of reducing sedentary behavior in metabolic health, possibly in addition to body mass index with a physically active lifestyle. 

P for trend=0.012

Fasting plasma insulin (pmol/L)

Quartiles of sedentary behavior
Summary: biological mechanisms

Energy expenditure/balance/flux

Body composition
- Fat mass (abdominal adiposity)
- Lean mass (skeletal muscle)
- Bone density

Metabolism
- Carbohydrate (glucose, insulin)
- Fat (triglycerides, lipoprotein lipase)
- Protein

Hemodynamic factors

Inflammation

Physical fitness & function

National Cancer Institute
Physical Activity Guidelines for Americans (2008): Adults

- **Avoid inactivity.** Some activity is better than none, more is better.

- **Health-enhancing physical activity** (added to baseline), produces health benefits.
  - **Aerobic activity**
    - Moderate intensity (150-300 min/wk)
    - Vigorous (75-150 min/wk)
  - **Strengthening** (2+ days/wk)

- **Baseline activity** refers to the light-intensity activities of daily life, such as standing, walking slowly, and lifting lightweight objects.

- We don't understand enough about whether doing more baseline activity results in health benefits.
New etiologic questions emerge

• Does sedentary behavior (sitting) displace time in baseline activities and increase risk?

• How much sitting is safe?

• How much, what types/intensities of activity are effective in reducing risk of too much sitting?
  – Exercise (MVPA) key, but,…
  – Is standing enough, or do you need do to move/walk?

• Are some kinds of sitting more/less deleterious than others?
  – Television, computer use vs. driving, reading?
Physical Activity Recommendation
WCRF/AICR 2007

“Be physically active as a part of everyday life”

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• The proportion of the population that is sedentary* to be halved every 10 years
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Personal Recommendations
• Be moderately physically active,…~brisk walk, 30 min/d
• As fitness improves, aim for…~2 x volume, mod. or vigorous
• Limit sedentary habits such as watching television
Thanks!