



Meeting 4

Cancer-Primary Prevention

Chair: Anne McTiernan

Members: Peter Katzmarzyk, Ken Powell

Experts and Consultants



- Consultant:
 - Christine M. Friedenreich, PhD, Alberta Health Services & University of Calgary
- ICF Staff:
 - Bethany Tennant, PhD
- HHS Staff:
 - Alison Vaux-Bjerke, MPH

Subcommittee Questions



1. What is the relationship between physical activity and specific cancer incidence?
 - Is there a dose-response relationship? If yes, what is the shape of the relationship?
 - Does the relationship vary by age, sex, race/ethnicity, socio-economic status, or weight status?
 - Does the relationship vary by specific cancer subtypes?
 - Is the relationship present in persons at high risk, such as those with familial predisposition to cancer?

2. What is the relationship between sedentary behavior and cancer incidence?

note: conclusions covered by Sedentary SC

Question #1

- What is the relationship between physical activity and specific cancer incidence?
- Source of evidence to answer question:
 - Systematic reviews
 - Meta-analyses
 - Pooled analyses

Analytical Framework

Systematic Review Question

What is the relationship between physical activity and specific cancer incidence?

Target Population

Adults, 18 years and older

Exposure

All types and intensities of physical activity, including lifestyle activities/leisure activities

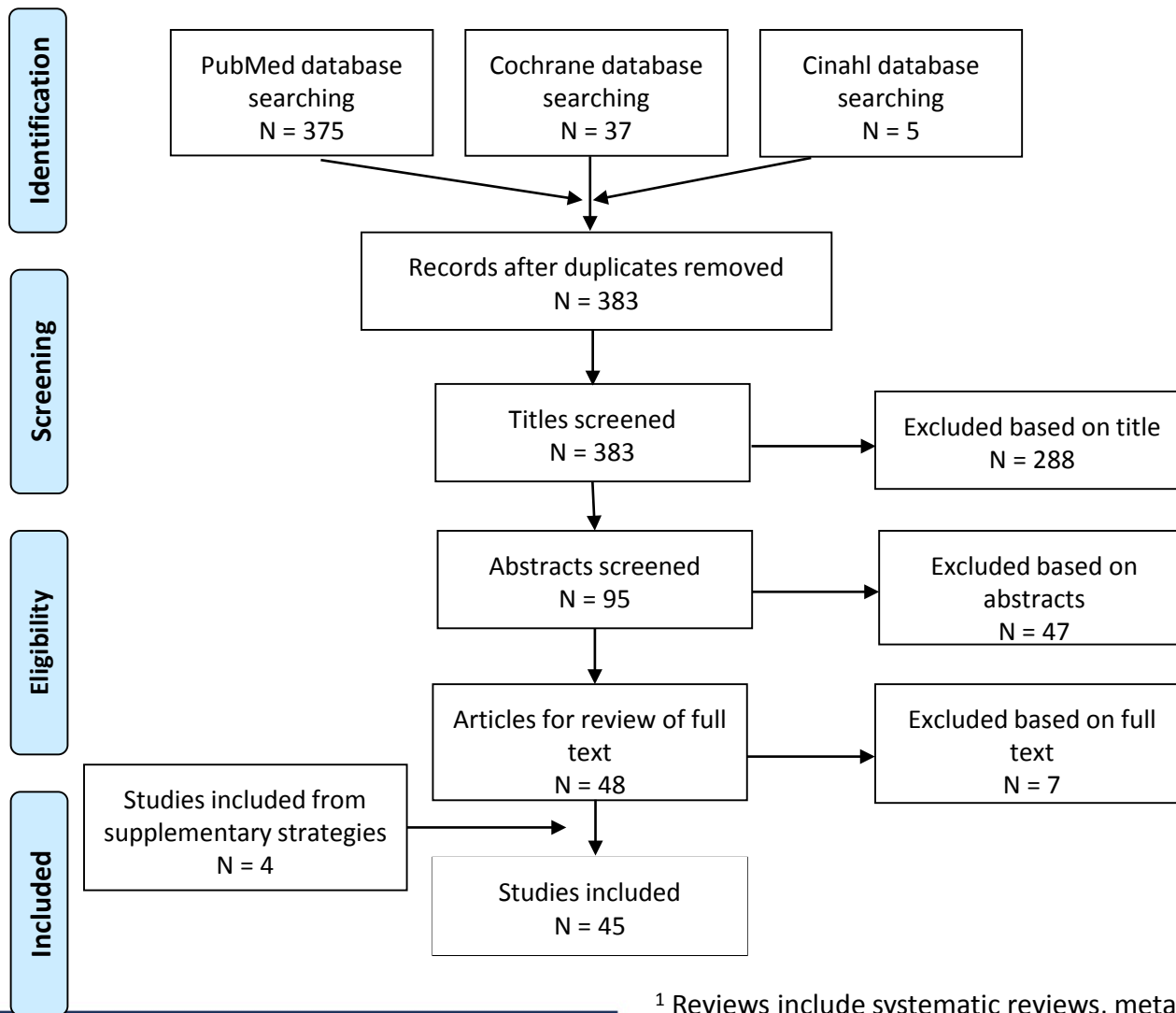
Comparison

Adults who participate in varying levels of physical activity

Endpoint Health Outcome

Incidence of cancer

Search Results (All Cancers): High-Quality Reviews¹ and Reports



¹ Reviews include systematic reviews, meta-analyses, and pooled analyses.

Evidence: Cancers, *Draft* Grades, Data Sources

Cancer	Grade	Number of Reviews
Physical activity protects:		
Breast*	Strong	6
Colon/Rectum*	Strong	8
Endometrium	Strong	5
Stomach	Strong	6
Esophagus (adenocarcinoma)	Strong	4
Bladder	Strong	2
Lung	Moderate	3
Pancreas	Limited	6
Head & Neck	Limited	2
Brain	Limited	2
Prostate	Limited	3
Ovary	Limited	4
Blood & lymphatics	Limited	5
No effect of physical activity:		
Thyroid	Moderate	3

* Breast and colon/rectum conclusions previously presented at PAGAC Meeting 3

Draft Key Findings – Endometrium

- 33 studies (15 cohort) in largest meta-analysis (Schmid 2015)
- “Highest” vs. “lowest” odds ratio (95% confidence intervals):
 - Total PA 0.80 (0.75-0.85)
 - Recreational 0.84 (0.78-0.91)
 - Occupational 0.81 (0.75-0.87)
 - Walking 0.82 (0.69-0.97)
- Dose-response relative risk (RR) vs. < 3 MET-hours/week
 - 3-8: 0.94
 - 9-20: 0.79
 - > 20: 0.87 (p non-linearity < 0.05)
- Effect by body mass index (BMI kg/m²)
 - < 25: 0.97 (0.84-1.13)
 - ≥ 25: 0.69 (0.52-0.91)

Draft Conclusion Statement - Endometrium

PA Parameter	Effect on Risk	Grade
“highest” vs. “lowest” PA	↓	Strong
Dose-response	↓	Moderate
Age	Insufficient evidence	Not assignable
Race/ethnicity	Insufficient evidence	Not assignable
Weight status	Greater ↓ for BMI > 25	Moderate
High risk persons	Insufficient evidence	Not assignable
Cancer subtype	Insufficient evidence	Not assignable

Draft Key Findings – Stomach (Gastric cardia & Non-cardia)

- 22 studies (10 cohort) in largest meta-analysis (Psaltopoulo 2016)
- “Highest” vs. “lowest” odds ratio:
 - Total PA 0.84 (0.73-0.96)
- Dose-response odds ratio vs. lowest tertile (Singh 2013)
 - Middle 0.91 (0.82-1.02)
 - Upper 0.78 (0.68-0.90)
- Gender: Inconsistent
- Race/ethnicity:
 - Inconsistent variability Asian vs. non-Asian
 - No other data
- Cancer subtypes:
 - Similar effects in gastric cardia & non-cardia

Draft Conclusion Statement - Stomach

PA Parameter	Effect on Risk	Grade
“highest” vs. “lowest” PA	↓	Strong
Dose-response	↓	Moderate
Age	Insufficient evidence	Not assignable
Race/ethnicity	Insufficient evidence	Not assignable
Weight status	Insufficient evidence	Not assignable
High risk persons	Insufficient evidence	Not assignable
Cancer subtype	↓ cardia ↓ non-cardia	Moderate

Draft Key Findings – Esophagus (Adenocarcinoma & Squamous)

- 24 studies (9 cohort) in largest meta-analysis (Behrens 2014)
- “Highest” vs. “lowest” odds ratio:
 - Adenocarcinoma, total PA 0.79 (0.66-0.94)
 - Squamous, total PA 0.94 (0.41-2.16)
- Dose-response odds ratio for all esophagus combined vs. lowest tertile (Singh 2014)
 - Middle 0.88 (0.70-1.1)
 - Upper 0.76 (0.60-0.97)
- Gender: Inconsistent
- Race/ethnicity:
 - Inconsistent variability Asian vs. non-Asian
 - No other data
- BMI: pooled cohort analysis (Moore 2016) – no effect

Draft Conclusion Statement - Esophagus

PA Parameter	Effect on Risk	Grade
“highest” vs. “lowest” PA	↓ adenocarcinoma	Strong
Dose-response	Insufficient evidence	Not assignable
Age	Insufficient evidence	Not assignable
Race/ethnicity	Insufficient evidence	Not assignable
Weight status	Insufficient evidence	Not assignable
High risk persons	Insufficient evidence	Not assignable
Sex	Insufficient evidence	Not assignable
Cancer subtype	↓ adenocarcinoma ↔ squamous cell	Limited

Draft Key Findings – Bladder

- 15 studies (9 cohort) in largest meta-analysis (Keimling 2014)
- “Highest” vs. “lowest” relative risk:
 - Total PA 0.85 (0.74-0.98)
- Dose-response relative risk vs. lowest quartile
 - Quartile 2: 0.90 (0.83-0.97)
 - Quartile 3: 0.86 (0.77-0.96)
 - Quartile 4: 0.83 (0.72-0.95)
- Gender
 - Female: relative risk 0.83 (0.73-0.94)
 - Male: relative risk 0.92 (0.82-1.05)

Draft Conclusion Statement - Bladder

PA Parameter	Effect on Risk	Grade
“highest” vs. “lowest” PA	↓	Strong
Dose-response	↓	Moderate
Age	Insufficient evidence	Not assignable
Race/ethnicity	Insufficient evidence	Not assignable
Weight status	Insufficient evidence	Not assignable
High risk persons	Insufficient evidence	Not assignable
Sex	↓ women ↔ men	Limited
Cancer subtype	Insufficient evidence	Not assignable

Draft Key Findings – Lung

- 28 studies (22 cohorts) in largest meta-analysis (Brenner 2016)
- “Highest” vs. “lowest” relative risk:
 - Total PA 0.74 (0.67-0.82)
- Dose-response: no data
- Gender: protective effect higher in female smokers than male smokers
- BMI: PA effect greater for $< 25 \text{ kg/m}^2$ vs. higher

Draft Conclusion Statement – Lung

PA Parameter	Effect on Risk	Grade
“highest” vs. “lowest” PA	↓	Moderate
Dose-response	↓	Limited
Age	Does not vary by age	Limited
Race/ethnicity	Insufficient evidence	Not assignable
Weight status	Greater ↓ for BMI < 25	Limited
High risk persons	Greater ↓ in current/former smokers	Limited
Sex	Greater in women	Limited
Cancer subtype	Does not vary	Limited

Draft Key Findings – Pancreas

- 22 cohort studies in largest meta-analysis (Behrens 2015)
- “highest” vs. “lowest” relative risk:
 - Leisure PA 0.93 (0.88-0.98)
 - Effect stronger in case-control than cohort studies
- Dose-response: no statistically significant dose-response observed
- Gender relative risk:
 - Female-only studies: 0.96 (0.90-1.03)
 - Male-only studies: 0.94 (0.86-1.02)
 - Studies with both genders combined: 0.82 (0.72-0.91)
- BMI (Moore pooled analysis 10 cohorts): adjustment did not alter associations

Draft Conclusion Statement - Pancreas

PA Parameter	Effect on Risk	Grade
“highest” vs. “lowest” PA	↓	Limited
Dose-response	Insufficient evidence	Not assignable
Age	Insufficient evidence	Not assignable
Race/ethnicity	Insufficient evidence	Not assignable
Weight status	Insufficient evidence	Not assignable
High risk persons	Insufficient evidence	Not assignable
Sex	Similar in women & men	Limited
Cancer subtype	Insufficient evidence	Not assignable

Draft Key Findings – Head & Neck (Oral Cavity, Larynx, Pharynx)



- Pooled 4 case-control studies
 - Oral cavity:
 - Moderate PA: OR=0.74 (0.56-0.97)
 - High PA: OR=0.53 (0.32-0.88)
 - Pharynx:
 - Moderate PA: OR=0.67 (0.53-0.85)
 - High PA: OR=0.58 (0.38-0.89)
 - Larynx:
 - Moderate PA: OR=0.81 (0.60-1.11)
 - High PA: OR=1.73 (1.04-2.88)
- Pooled 11 cohort studies, head & neck combined:
 - 90th vs 10th percentile:
 - HR=0.85 (0.78-0.93)

Draft Conclusion Statement – Head & Neck



PA Parameter	Effect on Risk	Grade
“highest” vs. “lowest” PA	↓	Limited
Dose-response	Insufficient evidence	Not assignable
Age	Insufficient evidence	Not assignable
Race/ethnicity	Insufficient evidence	Not assignable
Weight status	Insufficient evidence	Not assignable
High risk persons	Insufficient evidence	Not assignable
Sex	Similar in women & men	Limited
Cancer subtype	Insufficient evidence	Not assignable

Draft Key Findings – Brain (Glioma, Meningioma, Combined brain)

- 3 cohorts (glioma) & 4 cohorts (meningioma) (Niedermaier 2015)
- Highest vs lowest PA levels relative risk:
 - Meningioma 0.73 (0.61-0.88)
 - Glioma: 0.86 (0.76-0.97)
- BMI (Moore pooled analysis, 10 cohorts, all brain combined): adjustment did not alter associations
- No information available on specific brain cancers other than glioma and meningioma

Draft Conclusion Statement – Brain



PA Parameter	Effect on Risk	Grade
“highest” vs. “lowest” PA	↓ Glioma ↓ Meningioma	Limited
Dose-response	Insufficient evidence	Not assignable
Age	Insufficient evidence	Not assignable
Race/ethnicity	Insufficient evidence	Not assignable
Weight status	Insufficient evidence	Not assignable
High risk persons	Insufficient evidence	Not assignable
Sex	Insufficient evidence	Not assignable
Cancer subtype	Insufficient evidence	Not assignable

Draft Key Findings – Prostate



- 19 cohort studies in largest meta-analysis (Liu 2011)
- “highest” vs. “lowest” relative risk:
 - Total PA: 0.90 (0.84-0.95)
 - Occupational PA: 0.81 (0.73-0.91)
 - Recreational PA: 0.95 (0.89-1.00)
- Effect by subtype (Liu 2016, 18 cohorts)
 - Non-aggressive prostate cancer = 0.98 (0.79-1.21)
 - Aggressive prostate cancer = 0.89 (0.71-1.12)
- BMI (Moore pooled analysis, 7 cohorts): adjustment did not alter associations

Draft Conclusion Statement – Prostate



PA Parameter	Effect on Risk	Grade
“highest” vs. “lowest” PA	↓	Limited
Dose-response	Insufficient evidence	Not assignable
Age	Greater ↓ < 65 years	Limited
Race/ethnicity	Greater ↓ blacks vs. whites	Limited
Weight status	Insufficient evidence	Not assignable
High risk persons	Insufficient evidence	Not assignable
Cancer subtype	Greater ↓ aggressive vs. non-aggressive tumors	Limited

Draft Key Findings – Ovary



- 9 cohort studies in largest meta-analysis (Liu 2016)
 - “highest” vs. “lowest” hazard ratio:
 - Leisure PA 0.96 (95% CI 0.74-1.26)
- Dose-response: no statistically significant dose-response observed
- BMI (Moore pooled analysis 9 cohorts): adjustment did not alter associations

Draft Conclusion Statement – Ovary

PA Parameter	Effect on Risk	Grade
“highest” vs. “lowest” PA	↓	Limited
Dose-response	Insufficient evidence	Not assignable
Age	Insufficient evidence	Not assignable
Race/ethnicity	Insufficient evidence	Not assignable
Weight status	Insufficient evidence	Not assignable
High risk persons	Insufficient evidence	Not assignable
Cancer subtype	Insufficient evidence	Not assignable

Draft Key Findings – Blood

- Types of blood cancers in adults
 - Leukemias
 - Chronic myelogenous (CML)
 - Chronic lymphocytic (CLL), small lymphocytic lymphoma (SLL)
 - Acute myelogenous (AML)
 - Acute lymphocytic (ALL)
 - Lymphomas
 - Non-Hodgkins
 - Hodgkins
 - Multiple myeloma

“Highest” vs. “Lowest” Physical Activity & Blood Cancer Risk (Jochem 2014, 15 cohorts)

Type of Blood Cancer	Relative Risk
Non-Hodgkin’s lymphoma	0.91
Hodgkin’s lymphoma	0.86
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)	0.95
Diffuse large B-cell lymphoma	0.99
Follicular lymphoma	1.01
Leukemia	0.97
Multiple myeloma	0.86

- Moore, 9-11 cohorts: BMI adjustment did not affect results for leukemia, myeloma, non-Hodgkin’s lymphoma, lymphocytic leukemia

Draft Conclusion Statement – Blood

PA Parameter	Effect on Risk	Grade
“highest” vs. “lowest” PA	↓	Limited
Dose-response	Insufficient evidence by cancer type	Not assignable
Age	Insufficient evidence	Not assignable
Race/ethnicity	Insufficient evidence	Not assignable
Weight status	Insufficient evidence	Not assignable
High risk persons	Insufficient evidence	Not assignable
Sex	Variable by cancer type	Limited
Cancer subtype	PA effect seen in multiple cancer types	Limited

Draft Key Findings – Thyroid



- 8 cohort studies in largest meta-analysis (Schmid 2013)
 - “highest” vs. “lowest” relative risk:
 - Total PA 1.06 (95% CI 0.79-1.42)
- Dose-response (Kitihara 2013, 5 cohorts):
 - Low: 1.0 (reference)
 - Medium: 1.11 (0.92-1.33)
 - High: 1.18 (1.00-1.39)
 - P trend = 0.06
- BMI (Moore pooled analysis 11 cohorts): adjustment did not alter associations

Draft Conclusion Statement – Thyroid



PA Parameter	Effect on Risk	Grade
“highest” vs. “lowest” PA	↔	Moderate
Dose-response	Insufficient evidence	Not assignable
Age	Insufficient evidence	Not assignable
Race/ethnicity	Insufficient evidence	Not assignable
Weight status	Insufficient evidence	Not assignable
High risk persons	Insufficient evidence	Not assignable
Sex	Insufficient evidence	Not assignable
Cancer subtype	Insufficient evidence	Not assignable

Committee Discussion

- What is the relationship between physical activity and specific cancer incidence?
 - Is there a dose-response relationship? If yes, what is the shape of the relationship?
 - Does the relationship vary by age, sex, race/ethnicity, socio-economic status, or weight status?
 - Does the relationship vary by specific cancer subtypes?
 - Is the relationship present in persons at high risk, such as those with familial predisposition to cancer?

Next Steps

- Ensure consistency of evidence grading and finalize proposed grades
- Develop research recommendations
- Finalize draft of cancer chapter for PAGAC report