A layman's guide to reading medical research

Aurora Esquela Kerscher, Ph.D.

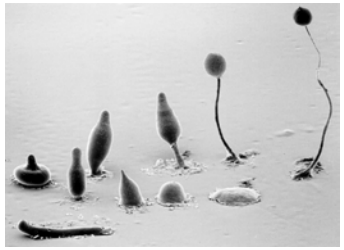
Eastern Virginia Medical School

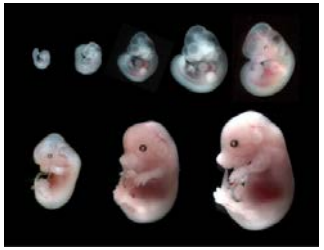
September 1, 2021

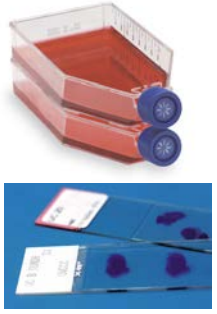
Active Surveillance Virtual Support Group of AnCan/UsToo

Genetic Research & Me

Disclaimer! I am not a clinician
but rather a developmental biology scientist by training.







Washington University in St. Louis

JOHNS HOPKINS MEDICINE

Yale

EVMS
Eastern Virginia Medical School

Welcome to my lab!

EVMS
Community Focus. World Impact.

Eastern Virginia Medical School
Norfolk, Virginia

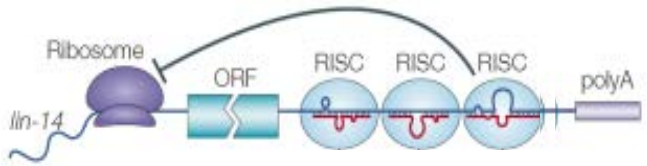
Kerscher Lab & Prostate Cancer

EVMS
Community Focus. World Impact.

Non-coding microRNAs

- Diagnostics
- Therapeutics

EVMS: one of largest urological biorepositories in the nation



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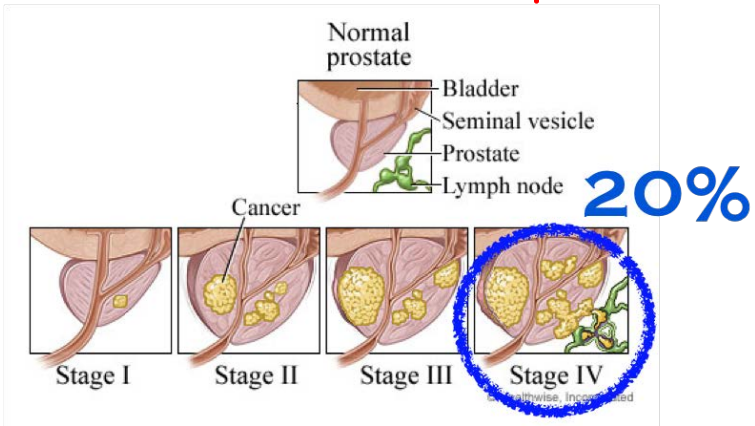
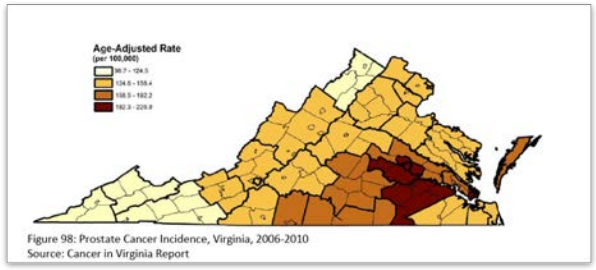


20%

PCa: 2nd leading cause male cancer deaths



Hampton Roads: one of highest PCa mortality rates in the nation

Kerscher Lab & Prostate Cancer

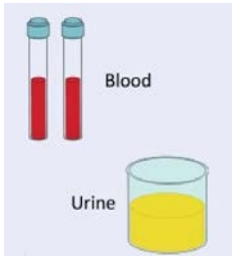
EVMS
Community Focus. World Impact.

Non-coding microRNAs

- **Diagnostics**
- Therapeutics

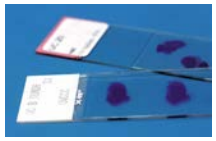
Biomarker discovery

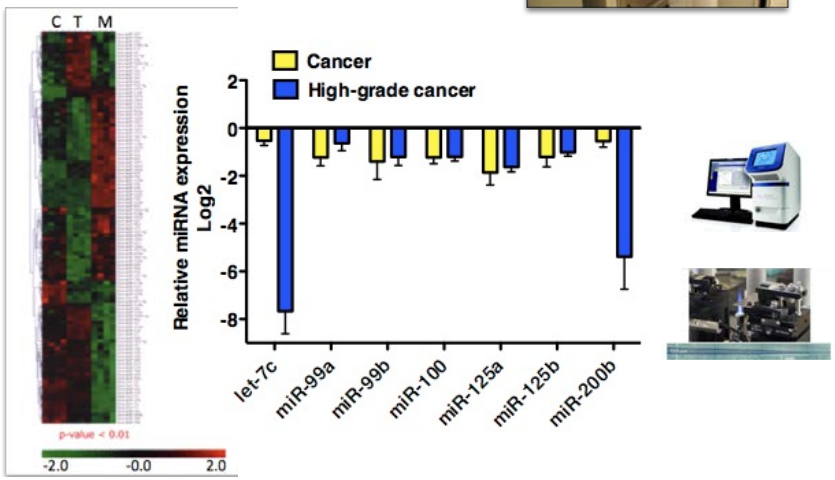
fluids



cell lines

tumors





Kerscher Lab & Prostate Cancer

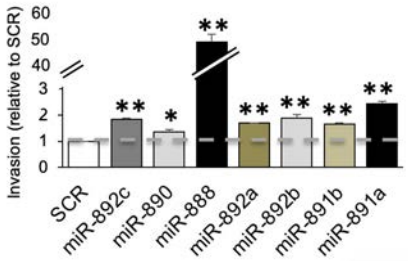
EVMS
Community Focus. World Impact.

Non-coding microRNAs

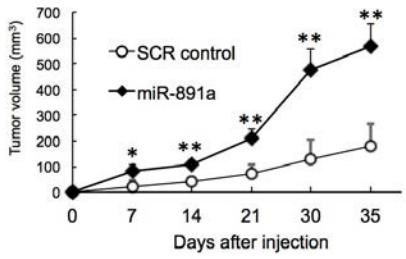
- Diagnostics
- **Therapeutics**

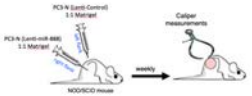
Aim to inactivate prostate oncogenic factors

Increased cell invasion

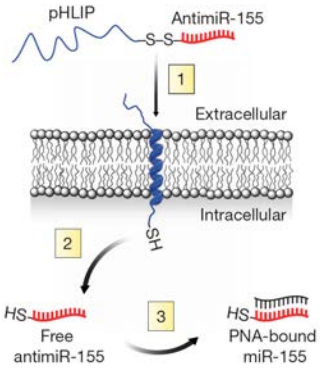


Increased tumor load in mice





Testing anti-microRNA reagents to block tumors



A layman's guide to reading medical research

Goal: Learn more about PCa research

- **Understand latest discoveries** (basic/translational research)
- **Educate/self-advocate** (clinical trials/treatment options, FDA approved, efficacy/side effects)

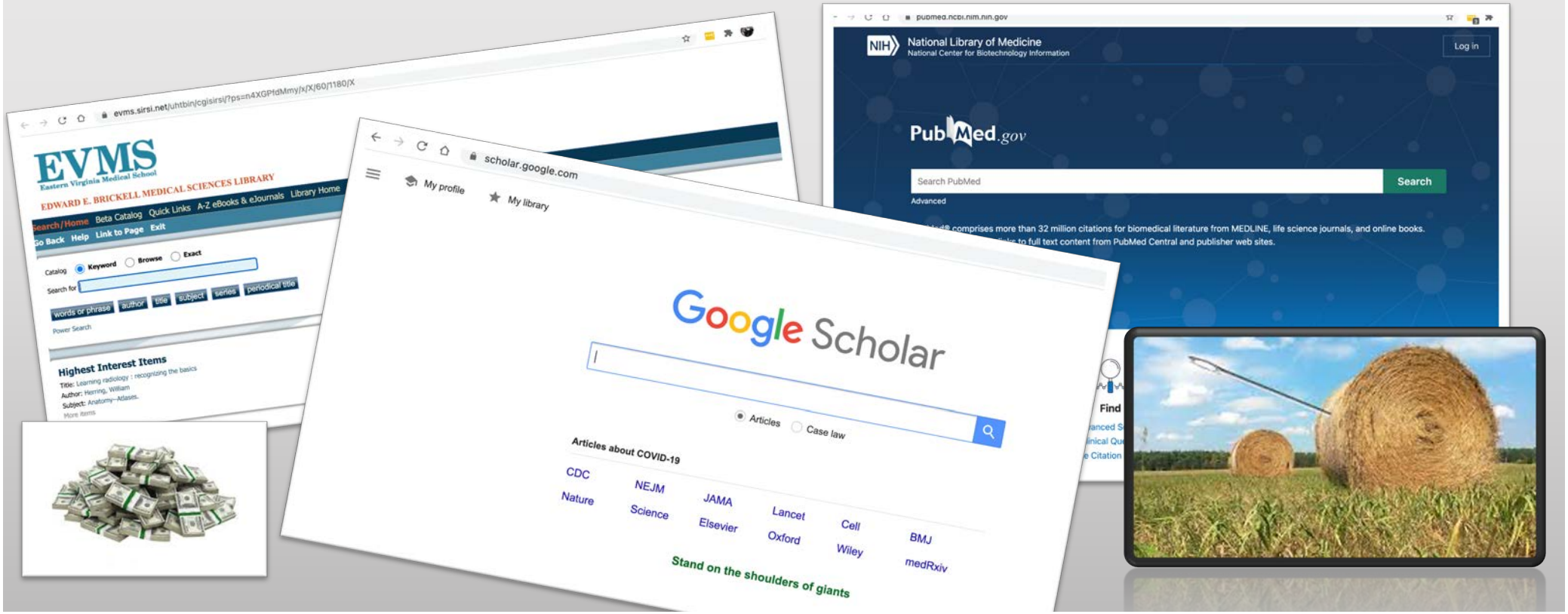
The Big Picture

Example cancer resources

- American Cancer Society: www.cancer.org/cancer/prostate-cancer
- Prostate Cancer Foundation: www.pcf.org/about-prostate-cancer
- National Cancer Institute: www.cancer.gov/types/prostate
- Mayo Clinic: www.mayoclinic.org/diseases-conditions/prostate-cancer/symptoms-causes/syc-20353087
- Johns Hopkins Medicine: www.hopkinsmedicine.org/health/conditions-and-diseases/prostate-cancer
- Wikipedia: not as your only resource
- **Scientific Research Literature: Reviews, Primary papers**

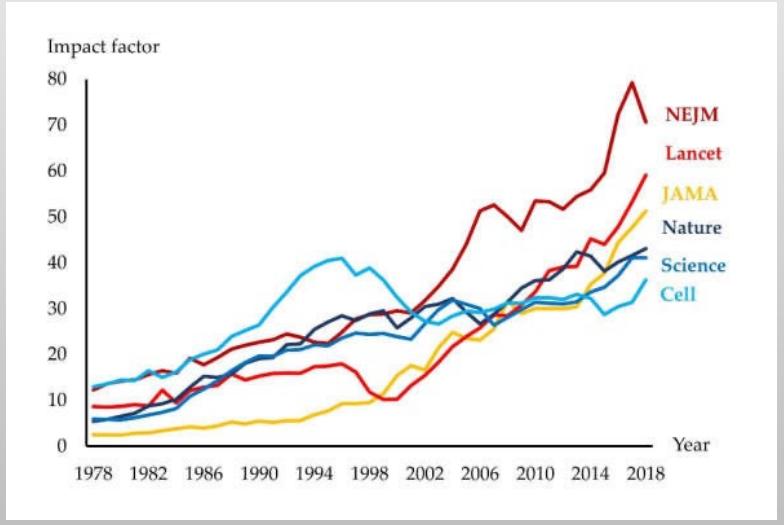
1st Challenge: Find the right paper!

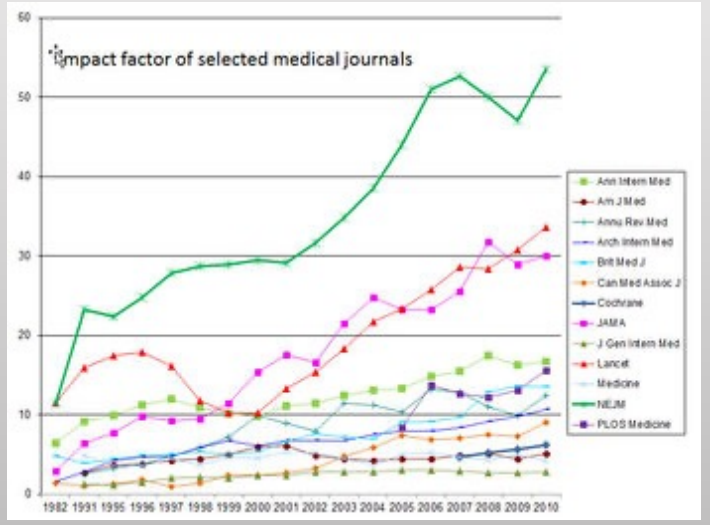
- Skim literature – use key words…*active surveillance, prostate cancer imaging screening, prostate cancer therapy, biochemical recurrence, castration resistance, metastasis*



Considerations…Impact Factor

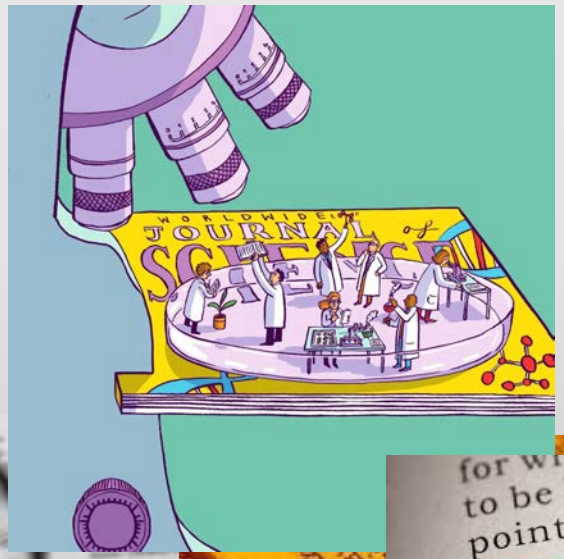
- A measure of the yearly mean number of citations of articles published in the last two years in a given journal.
- Frequently used as gauge for importance of a journal to its field.





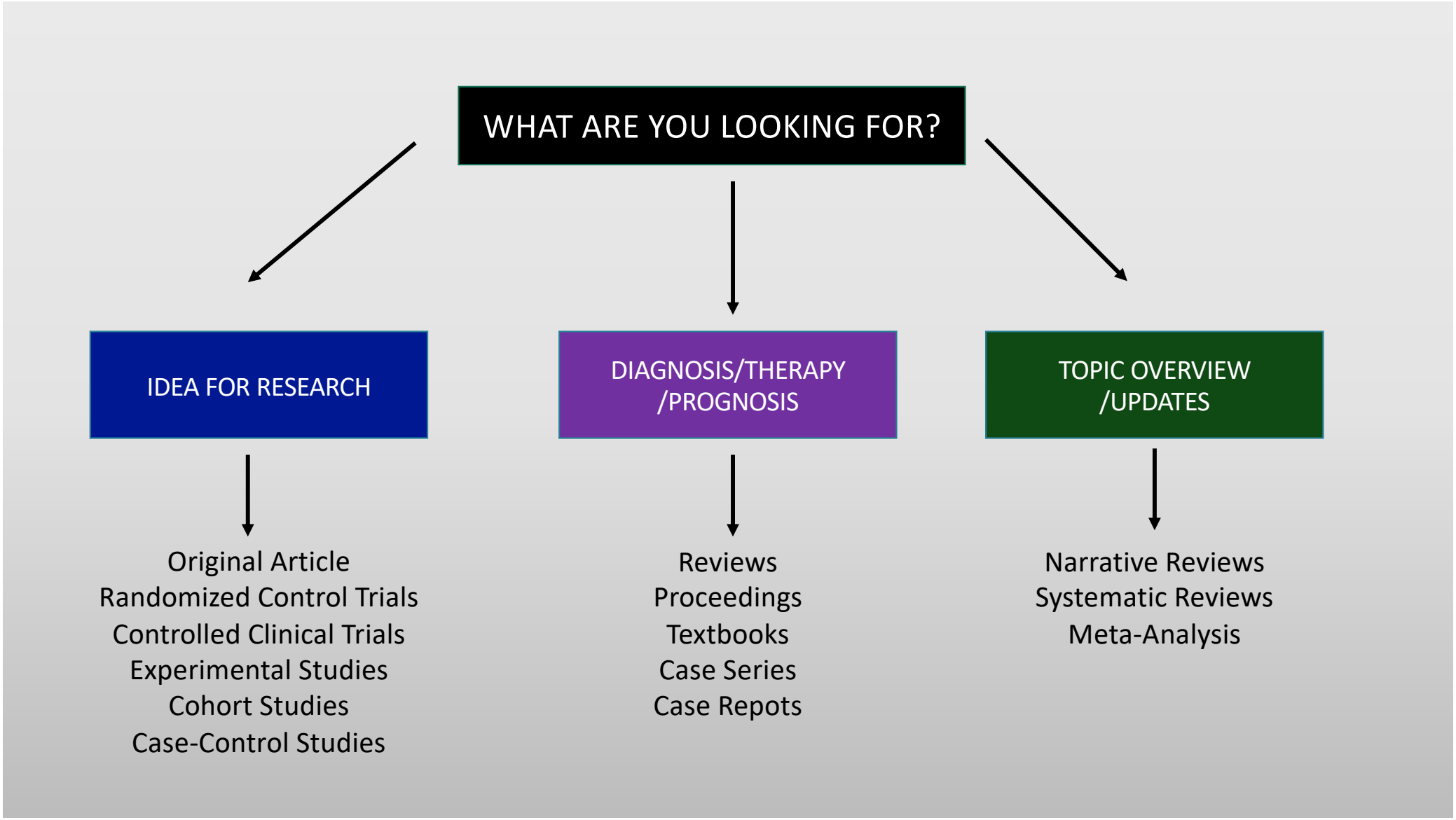
2nd Challenge: Understand the paper!

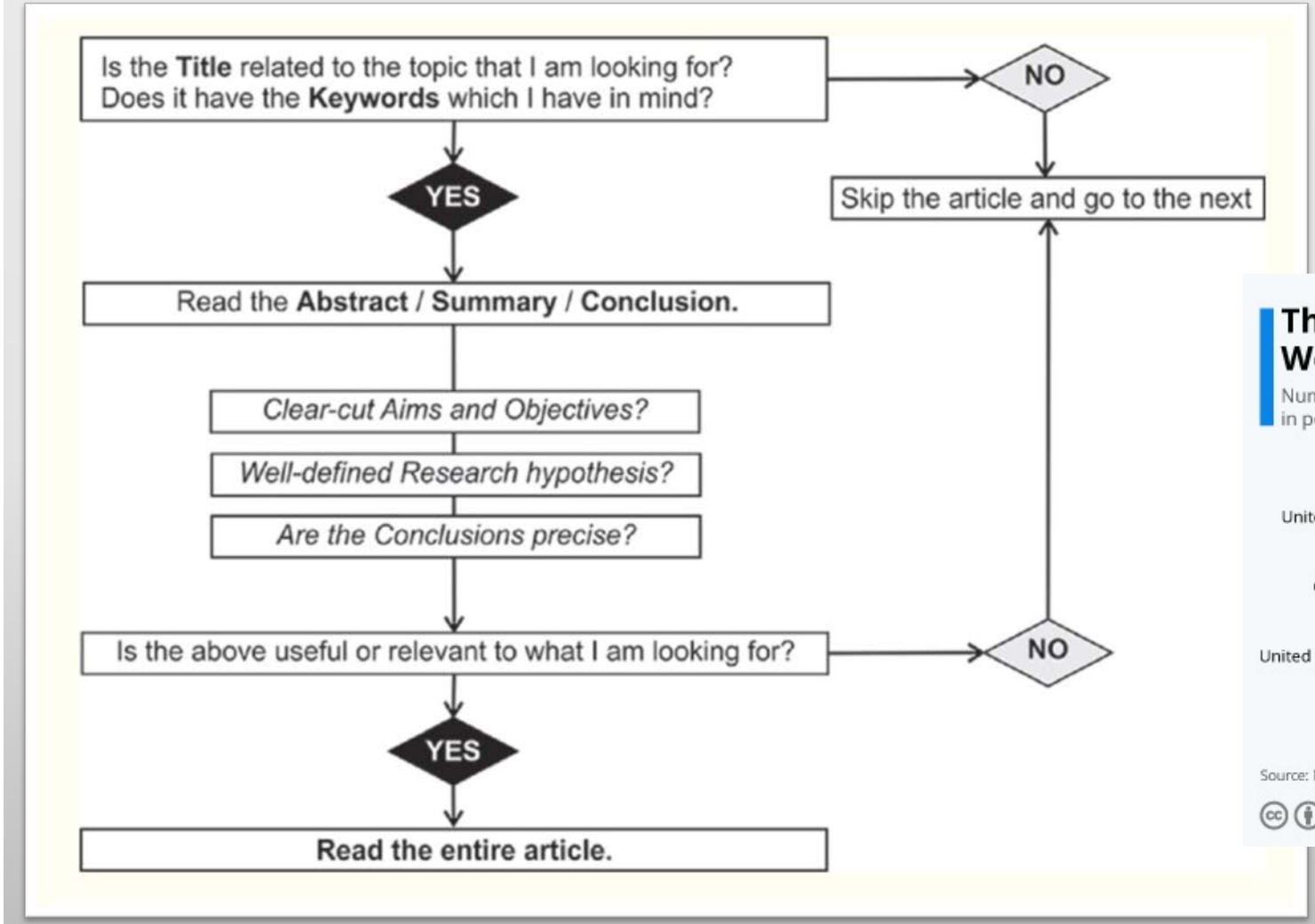
- Science literature is not necessary beautifully written literature.
- In many cases – it is like reading a completely different language!

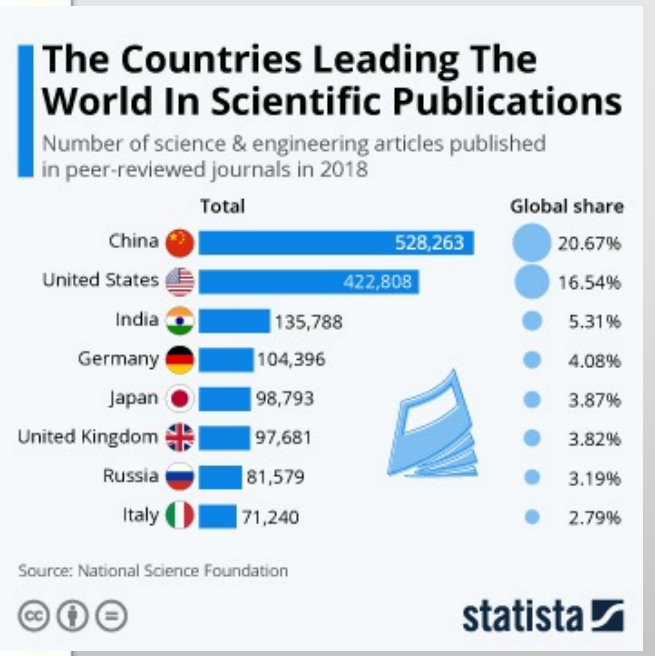


Why are you reading this scientific paper?

A. Educate/ Self-advocate re. medical care
B. Keep up with new scientific advances
C. Need to present a paper for journal club
D. Writing a review of about the field
E. Learn a new scientific method for lab


WHAT ARE YOU LOOKING FOR?
IDEA FOR RESEARCH
DIAGNOSIS/THERAPY /PROGNOSIS
TOPIC OVERVIEW /UPDATES
Original Article
Randomized Control Trials
Controlled Clinical Trials
Experimental Studies
Cohort Studies
Case-Control Studies
Reviews
Proceedings
Textbooks
Case Series
Case Repots
Narrative Reviews
Systematic Reviews
Meta-Analysis


Is the **Title** related to the topic that I am looking for?
Does it have the **Keywords** which I have in mind?
NO
YES
Skip the article and go to the next
Read the **Abstract / Summary / Conclusion.**
Clear-cut Aims and Objectives?
Well-defined Research hypothesis?
Are the Conclusions precise?
Is the above useful or relevant to what I am looking for?
NO
YES
Read the entire article.


The Countries Leading The World In Scientific Publications
Number of science & engineering articles published in peer-reviewed journals in 2018
Total
Global share
China 528,263 20.67%
United States 422,808 16.54%
India 135,788 5.31%
Germany 104,396 4.08%
Japan 98,793 3.87%
United Kingdom 97,681 3.82%
Russia 81,579 3.19%
Italy 71,240 2.79%
Source: National Science Foundation
statista

Our Case study

Research

*Thanks to:
Howard Wolinsky

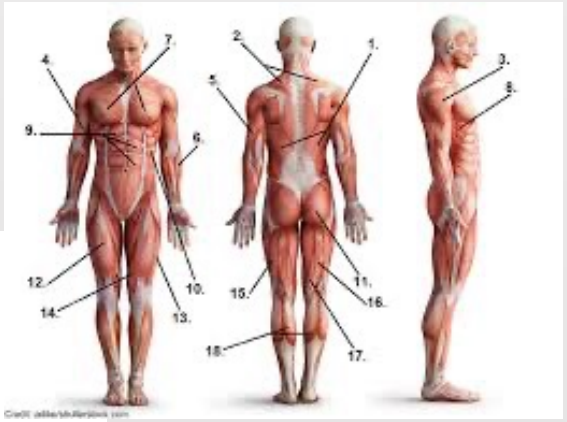
JAMA Oncology | Original Investigation

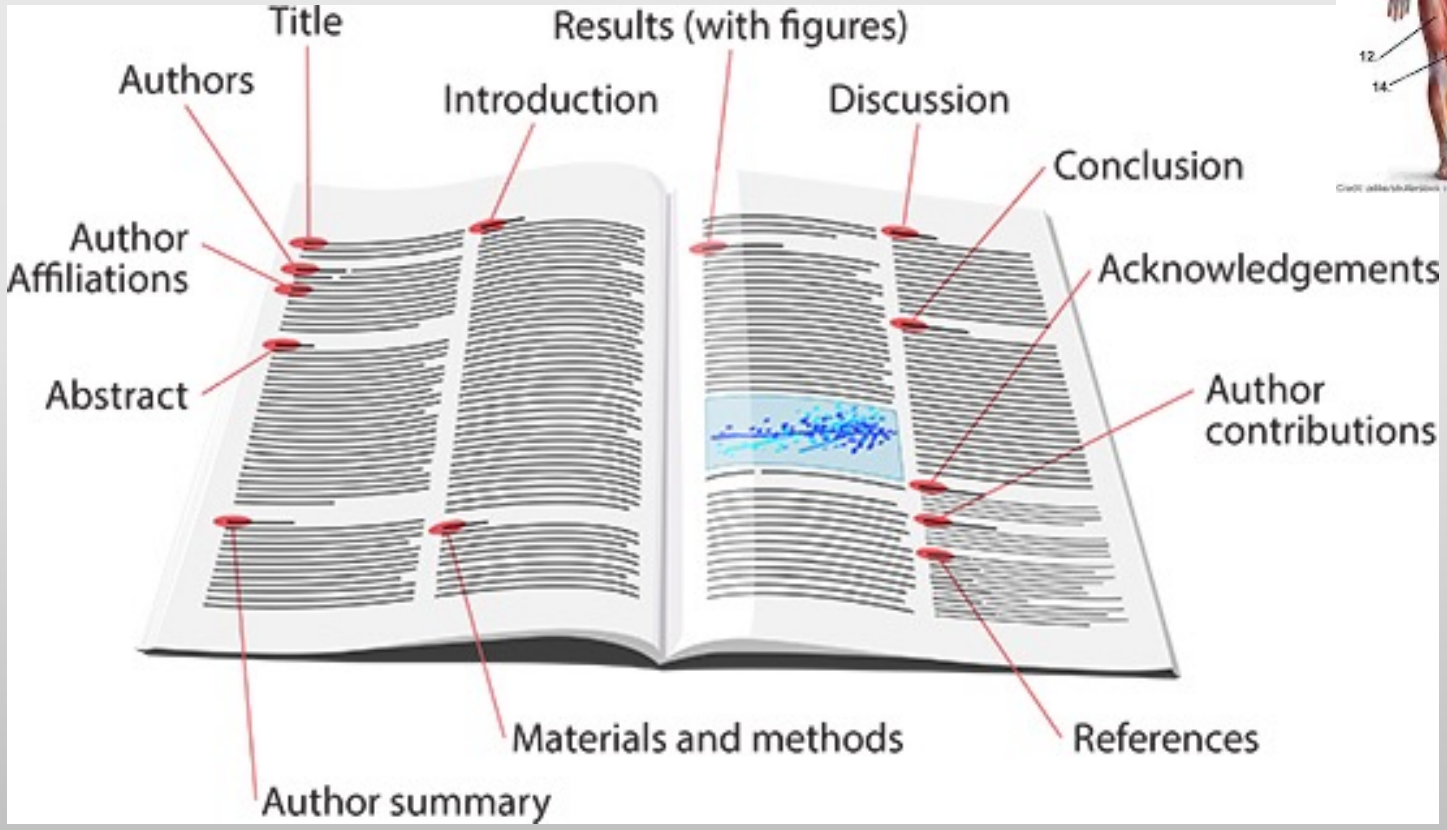
Effects of Exercise on Cardiorespiratory Fitness and Biochemical Progression in Men With Localized Prostate Cancer Under Active Surveillance
The ERASE Randomized Clinical Trial

Dong-Woo Kang, PhD; Adrian S. Fairey, MD; Normand G. Boulé, PhD; Catherine J. Field, PhD; Stephanie A. Wharton, BSc; Kerry S. Courneya, PhD

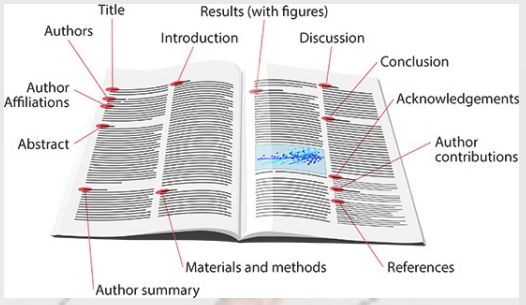
JAMA Oncology Published online August 19, 2021

Anatomy of a Research Paper





The typical “anatomy” of a paper



- **Title:** Topic and information about the authors
- **Abstract:** Brief overview
- **Keywords:** 4 or 5 words provided by the author (text search)
- **Introduction:** Background information and statement of hypothesis
- **Materials & Methods:** Details of how the study was conducted, procedures followed, instruments used and variables measured
- **Results:** All data of the study along with figures, tables and/or graphs
- **Discussion:** Interpretation of the results and implications of the study
- **References:** Citations of sources from where the information was obtained
- **Acknowledgements**
- **Supplemental Data/Methods** – details/controls

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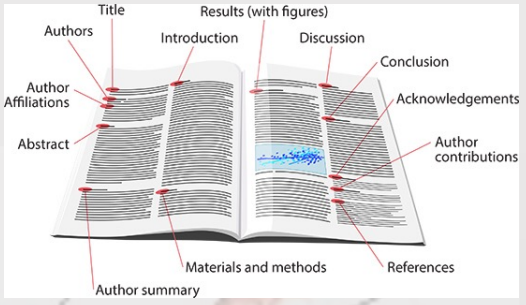

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- **References:** Citations of sources from where the information was obtained
- **Acknowledgements**
- **Supplemental Data / Methods** – details/controls

How do you Read a Research Paper?
Answer: Not necessarily in order!

What is the first thing you read when assigned a scientific paper?

A. Abstract
B. Introduction
C. Results
D. Figures
E. Discussion
F. The whole paper from beginning to end

What is the second thing you read when assigned a scientific paper?

A. Abstract
B. Introduction
C. Results
D. Figures
E. Discussion
F. The whole paper from beginning to end

Step by step to quickly read a research paper

Skim the Abstract

Read the Conclusion

Read the Results

Read the Methods

Repeat with next paper

Drew Dennis

https://medium.com/@drewdennis/how-to-read-scientific-papers-quickly-efficiently-e7030c4018fa

Step by step to quickly read/skim a research paper

Aurora Kerscher

Skim the Abstract

Read 1st & last paragraph of Introduction

Flip through Figures

Skim 1st & last paragraph of Conclusion

Repeat with next paper

How many times do you need to go through a scientific paper to understand it?

A. Once, very carefully
B. 2 times
C. 3 times
D. Countless, with notes

How many times do you need to go through a scientific paper to understand it?

A. Once, very carefully
B. 2 times
C. 3 times
D. Countless, with notes

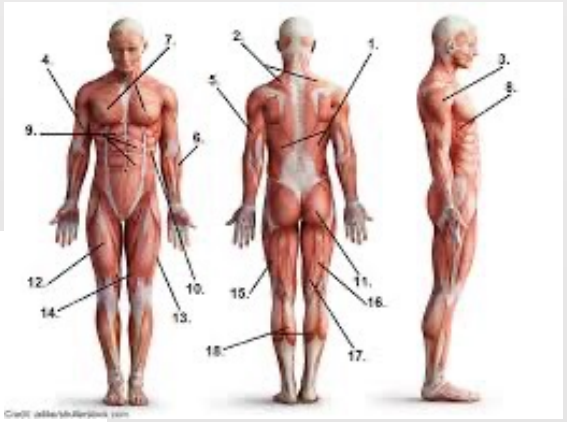
ANSWER: YES!
and depends…

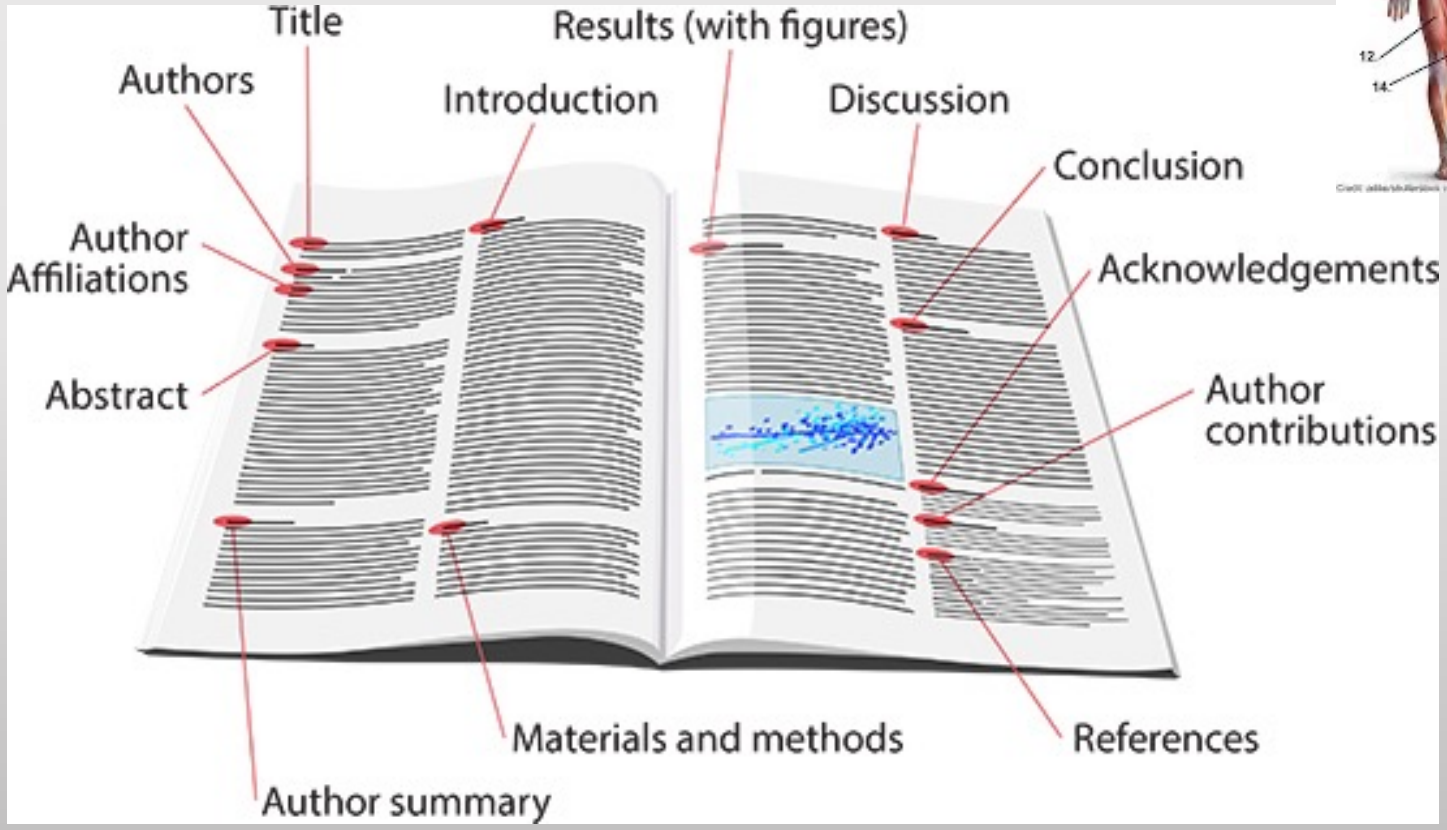
Reading a Paper Critically

- Understand the problem
- Understand the proposed solution
- Understand competing approaches / designs
- Evaluate the paper

- Peer review is the cornerstone of the scientific publishing process

Anatomy of a Research Paper





Title and Authors

- **Title** is very descriptive (often states the main finding) and is not about being creative and "catchy"!
- A good title will inform the potential reader a great deal about the study to decide whether to go ahead with the paper or dismiss it.
- **Order of Authors** is important. What can you tell from it? *1st author did all the work, last author is the boss.*

Example:

Research

JAMA Oncol. doi:10.1001/jamaoncol.2021.3067
Published online August 19, 2021.

JAMA Oncology | **Original Investigation**

Effects of Exercise on Cardiorespiratory Fitness and Biochemical Progression in Men With Localized Prostate Cancer Under Active Surveillance
The ERASE Randomized Clinical Trial

Dong-Woo Kang, PhD; Adrian S. Fairey, MD; Normand G. Boulé, PhD; Catherine J. Field, PhD; Stephanie A. Wharton, BSc; Kerry S. Courneya, PhD

Corresponding Author: Kerry S. Courneya, PhD, Faculty of Kinesiology, Sport, and Recreation, University of Alberta, 1-113 University Hall, Edmonton, Alberta T6G 2H9, Canada

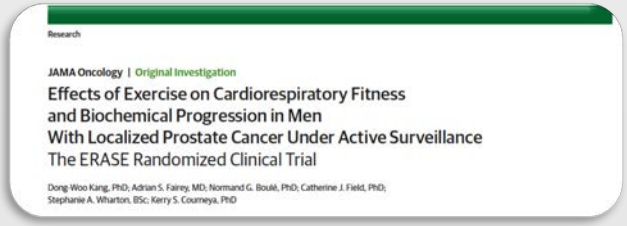
Abstract

- Very Dense - sometimes hard to read…
- Background
- Purpose of study
- Major findings
- Context of findings with state of the field right now
- *Helps us determine whether we should read the entire article or not.*

Abstract is what you see when you do a PubMed search. (Abstract is a free teaser!)

NCBI
PubMed.gov
US National Library of Medicine
National Institutes of Health

Clinical Abstract



Research

JAMA Oncology | Original Investigation

Effects of Exercise on Cardiorespiratory Fitness and Biochemical Progression in Men With Localized Prostate Cancer Under Active Surveillance
The ERASE Randomized Clinical Trial

Dong-Woo Kang, PhD; Adrian S. Fairey, MD; Normand G. Boulé, PhD; Catherine J. Field, PhD; Stephanie A. Wharton, BSc; Kerry S. Courneya, PhD

IMPORTANCE Men with prostate cancer who are undergoing active surveillance are at an increased risk of cardiovascular death and disease progression. Exercise has been shown to improve cardiorespiratory fitness, physical functioning, body composition, fatigue, and quality of life during and after treatment; however, to date only 1 exercise study has been conducted in this clinical setting.

OBJECTIVE To examine the effects of exercise on cardiorespiratory fitness and biochemical progression in men with prostate cancer who were undergoing active surveillance.

DESIGN, SETTING, AND PARTICIPANTS The Exercise During Active Surveillance for Prostate Cancer (ERASE) trial was a single-center, 2-group, phase 2 randomized clinical trial conducted at the University of Alberta, Edmonton, Canada. Eligible patients were recruited from July 24, 2018, to February 5, 2020. Participants were adult men who were diagnosed with localized very low risk to favorable intermediate risk prostate cancer and undergoing active surveillance. They were randomized to either the high-intensity interval training (HIIT) group or usual care group. All statistical analyses were based on the intention-to-treat principle.

INTERVENTIONS The HIIT group was asked to complete 12 weeks of thrice-weekly, supervised aerobic sessions on a treadmill at 85% to 95% of peak oxygen consumption (Vo_2). The usual care group maintained their normal exercise levels.

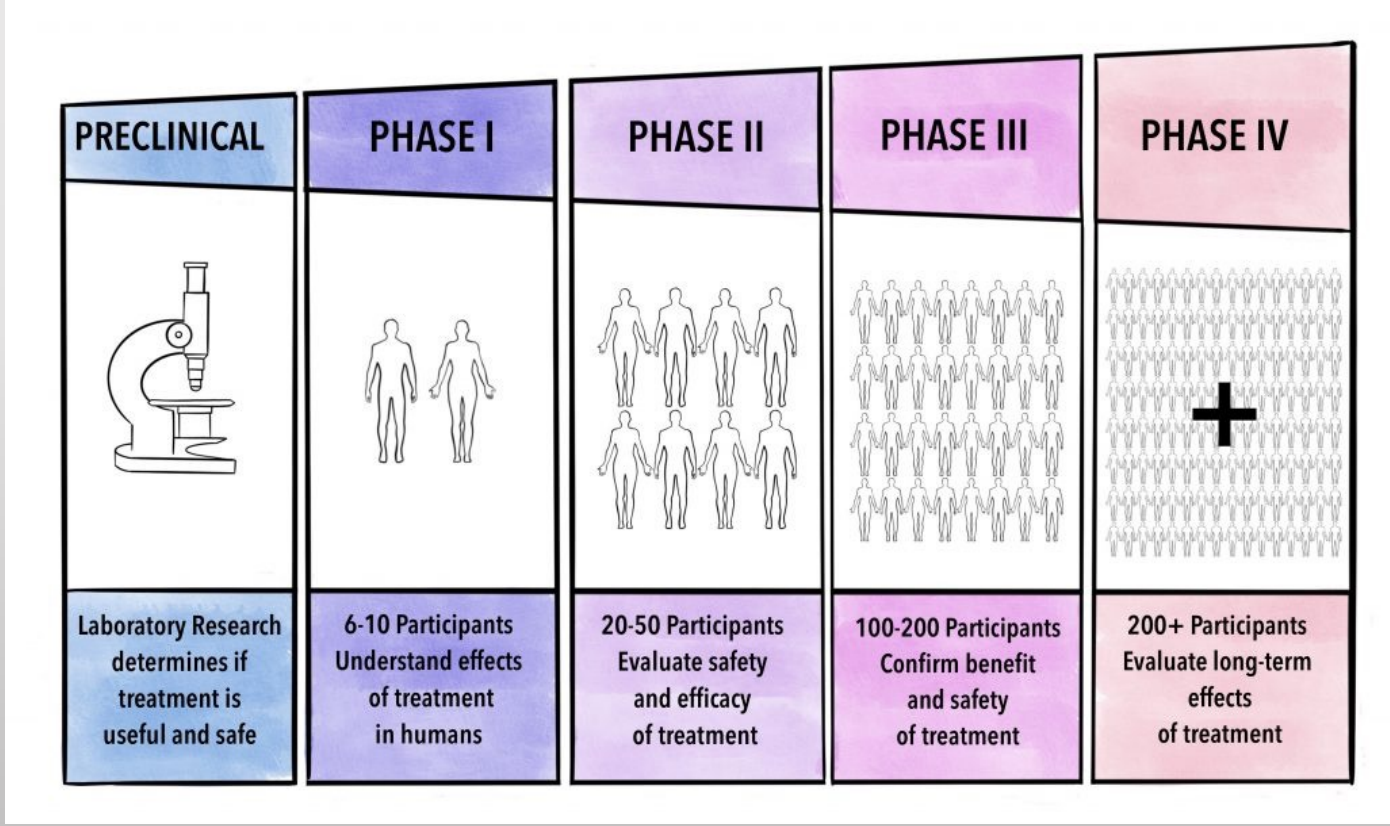
1

2

SCAN for information

- **What?** AS patients risk cardiovascular death/advanced PCa. Exercise improves CV.
- **Why?** Only 1 other study. Test if exercise can improve CV and PCa….*New therapy?*
- **How?** Randomized Clinical Trial for AS men (12 wks exercise versus no exercise).
- **Unclear Jargon:** *Phase 2 Clinical Trial, Vo_2,* Abbreviations (HIIT, ERASE)

Clinical Trial Phases



VO_2 max = maximum milliliters of oxygen consumed in 1 minute / body weight in kilograms

MAIN OUTCOMES AND MEASURES The primary outcome was peak $\dot{V}O_2$, which was assessed as the highest value of oxygen uptake during a graded exercise test using a modified Bruce protocol. Secondary and exploratory outcomes were indicators of biochemical progression of prostate cancer, including prostate-specific antigen (PSA) level and PSA kinetics, and growth of prostate cancer cell line LNCaP.

RESULTS A total of 52 male patients, with a mean (SD) age of 63.4 (7.1) years, were randomized to either the HIIT (n = 26) or usual care (n = 26) groups. Overall, 46 of 52 participants (88%) completed the postintervention peak $\dot{V}O_2$ assessment, and 49 of 52 participants (94%) provided blood samples. Adherence to HIIT was 96%. The primary outcome of peak $\dot{V}O_2$ increased by 0.9 mL/kg/min in the HIIT group and decreased by 0.5 mL/kg/min in the usual care group (adjusted between-group mean difference (1.6 mL/kg/min; 95% CI, 0.3-2.9; P = .01). Compared with the usual care group, the HIIT group experienced decreased PSA level (−1.1 µg/L; 95% CI, −2.1 to 0.0; P = .04), PSA velocity (−1.3 µg /L/y; 95% CI, −2.5 to −0.1; P = .04), and LNCaP cell growth (−0.13 optical density unit; 95% CI, −0.25 to −0.02; P = .02). No statistically significant differences were found in PSA doubling time or testosterone.

CONCLUSIONS AND RELEVANCE The ERASE trial demonstrated that HIIT increased cardiorespiratory fitness levels and decreased PSA levels, PSA velocity, and prostate cancer cell growth in men with localized prostate cancer who were under active surveillance. Larger trials are warranted to determine whether such improvement translates to better longer-term clinical outcomes in this setting.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03203460

SCAN for information

- **Method? M**easure VO_2, PSA, PSA kinetics, PCa cell growth.
- **Results/Conclude?** HIIT group (n=26) showed increased VO2. Showed decreased PSA, PSA kinetics, PCa cell growth compared to control group.
- **Limitations?** Need larger trial to see if show long-term clinical outcomes.

Basic Science Abstract

[Cell Cycle 7:6, 759-764; 15 March 2008]; ©2008 Landes Bioscience

Priority Report

The *let-7* microRNA reduces tumor growth in mouse models of lung cancer

MicroRNAs have been increasingly implicated in human cancer and interest has grown about the potential to use microRNAs to combat cancer. Lung cancer is the most prevalent form of cancer worldwide and lacks effective therapies. Here we have used both in vitro and in vivo approaches to show that the *let-7* microRNA directly represses cancer growth in the lung. We find that *let-7* inhibits the growth of multiple human lung cancer cell lines in culture, as well as the growth of lung cancer cell xenografts in immunodeficient mice. Using an established orthotopic mouse lung cancer model, we show that intranasal *let-7* administration reduces tumor formation in vivo in the lungs of animals expressing a G12D activating mutation for the *K-ras* oncogene. These findings provide direct evidence that *let-7* acts as a tumor suppressor gene in the lung and indicate that this miRNA may be useful as a novel therapeutic agent in lung cancer.

1

2

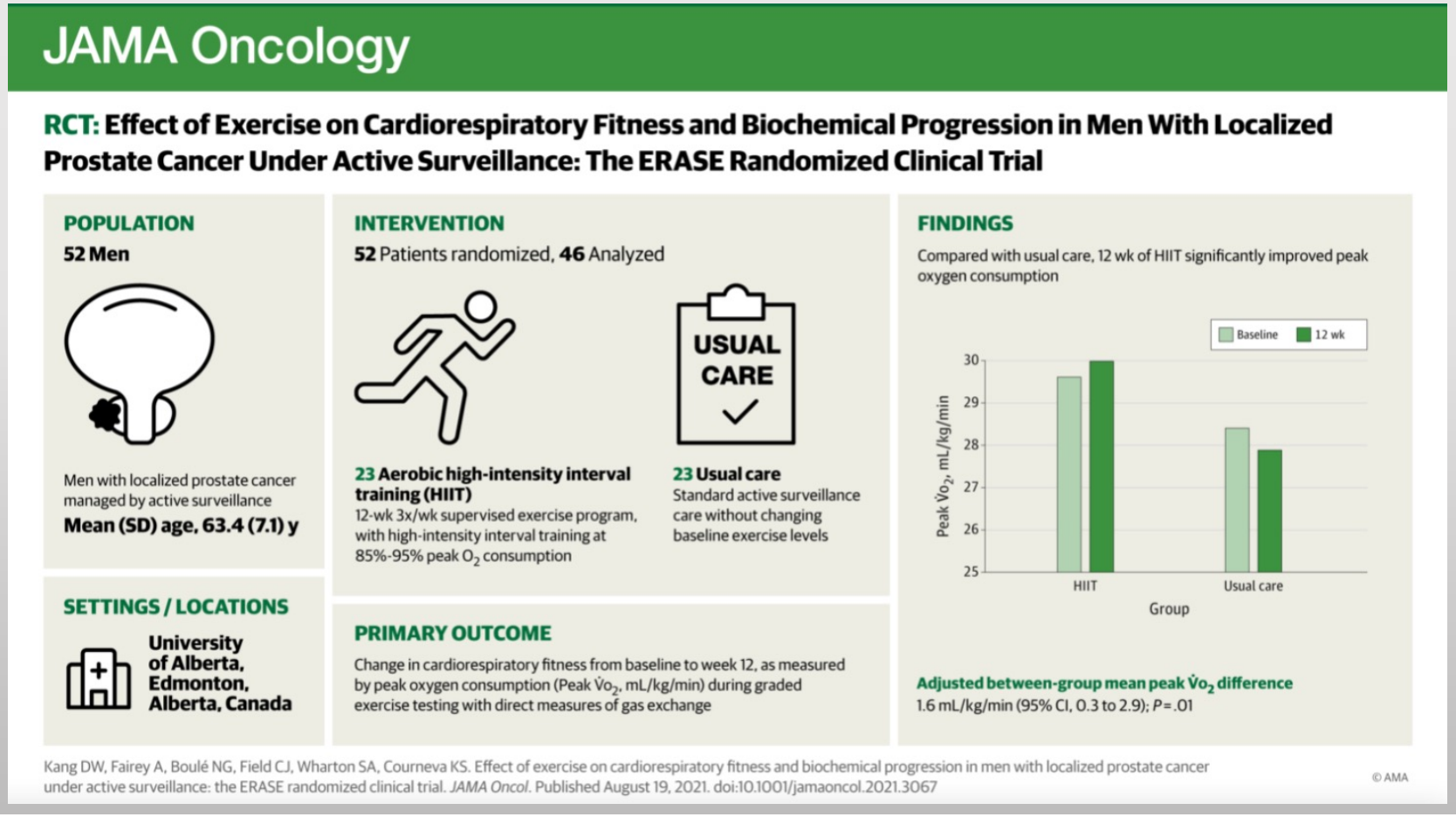
3

SCAN for information

- **What:** MicroRNAs (*let-7*) & lung cancer
- **Why:** Test if can repress lung tumor growth….*New therapeutic?*
- **How:** Use cell lines, mouse xenografts & orthotopic models
- **Unclear Jargon:** *What is up with G12D and Kras oncogene?*

What? Why? How? Results? Conclude?

Visual Abstract – best addition ever!



Key Points – 2nd best addition ever!

Key Points

Question Does a high-intensity interval training program improve cardiorespiratory fitness and delay the biochemical progression of prostate cancer in patients who are undergoing active surveillance?

Findings In this randomized clinical trial of 52 male participants with prostate cancer under active surveillance, 12 weeks of high-intensity interval training significantly improved peak oxygen consumption, decreased prostate-specific antigen levels, and decreased prostate-specific antigen velocity compared with usual care. It also inhibited the growth of prostate cancer cell line LNCaP in this patient population.

Meaning The findings of this study indicate that exercise may be an effective intervention for improving cardiorespiratory fitness and suppressing the progression of prostate cancer for patients undergoing active surveillance.

HYPOTHESIS of study

Identify the BIG QUESTION

- Ask yourself – **WHAT IS THE BIG QUESTION?**
  - What problem is being addressed?
- Then ask yourself – **Why should I care?**
  - How will the authors finding impact the field or clinical care?

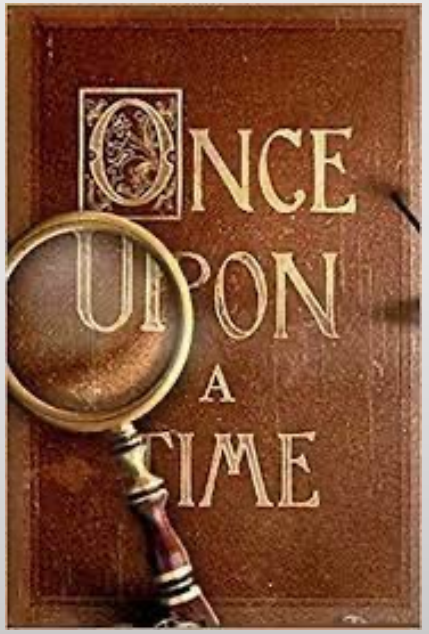
Hypothesis: Does a high-intensity exercise program improve cardiorespiratory fitness and delay prostate cancer progression in AS patients?

If true – this is an affordable way to manage cardiorespiratory health and cancer!

Introduction

- Provides **Background Information** for a fellow scientist (possibly in another field) to understand rationale and significance of study.
- Structure is usually:
  - **Gap in Knowledge:** Accepted state of knowledge in the
  - **Rationale:** Study focus is on a particular aspect of the field, often previous data that led directly to the work of this paper
  - **Hypothesis** being tested
  - **Conclusion** (Scientists don't like surprise endings)

- **TIP**: Skipping to last paragraph of Introduction usually will give you gist of hypothesis/aims/conclusion…



Introduction

An increasing number of men with low- to intermediate risk prostate cancer receive active surveillance as a primary management strategy.[1] Advantages of active surveillance include avoiding immediate radical treatments without compromising survival[2,3] and reducing treatment-related medical costs.[4,5] Men with prostate cancer who are on active surveillance have approximately 3 times higher risk of cardiovascular disease (CVD)-related death than prostate cancer-specific death.[2] Moreover, approximately 30% of men on active surveillance will ultimately experience disease progression and require radical treatment within 3 years, and 55% will need it within 10 years.[2] Interventions during active surveillance to boost cardiovascular health, delay disease progression, and precondition these men for possible radical treatments would be desirable.

The Problem

- Can exercise boost CV health, delay disease in Active Surveillance patients?

Rationale 1

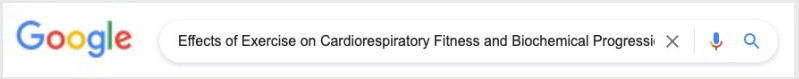
Research has shown that exercise improves cardiorespiratory fitness, physical functioning, body composition, fatigue, and quality of life during and after radical prostate cancer treatments.[6] Moreover, 2 aerobic exercise has been found to suppress the progression of prostate tumors and metastasis in animal models[7] and to enhance the biochemical outcomes of prostate cancer growth in humans.[8,9] Furthermore, higher levels of physical fitness and functioning during active surveillance may ease adverse effects and lead to better cancer-related outcomes after radical treatments.[10,11] To our knowledge, however, only 1 clinical trial has examined the feasibility of exercise in men on active surveillance, and no trial has investigated the efficacy of an isolated exercise intervention during active surveillance.[12] In this Exercise During Active Surveillance for Prostate Cancer (ERASE) trial,[13] we aimed to examine the effects of exercise on cardiorespiratory fitness and biochemical progression in men with prostate cancer who were undergoing active surveillance. We hypothesized that high-intensity interval training (HIIT) would generate substantial improvements in both health-related fitness and biochemical progression of prostate cancer in men on active surveillance compared with patients receiving usual care.

Gap in knowledge

Hypothesis

If you come across scientific jargon you don't understand, what do you do?

A. Skip word and figure it out due to context of paper
B. Google/Wikipedia/PubMed as I read
C. Write word in margin to look up later
D. Skim paper to look for author's definition
E. Ask a colleague
F. Grab previous notes…(lecture notes)



Diving deeper

- Google key words/terms and find quick answer
- Look up the references cited in paper
- Read a review – fastest way to catch up on a field (Make sure review is recent because science/tech moves quickly)
- Look up commentary about the paper (Google article title)

Google Effects of Exercise on Cardiorespiratory Fitness and Biochemical Progressi

Commentary about the paper: pre-digested

Invited Commentary

ONLINE FIRST

August 19, 2021

The Power of Exercise to Influence Cardiovascular and Oncologic Outcomes—Survival of the Fittest

Neha Vapiwala, MD[1]

» Author Affiliations | Article Information

JAMA Oncol. Published online August 19, 2021. doi:10.1001/jamaoncol.2021.3065

Oncology > Prostate Cancer

Can Working Out Slow Prostate Cancer Progression?

— Intense exercise improved markers of biochemical progression in patients on active surveillance

by Mike Bassett, Staff Writer, MedPage Today August 19, 2021

Renal & Urology News

PROSTATE CANCER ED CKD UROLOGY NEPHROLOGY MY

August 27, 2021

Exercise Found to Slow Biochemical Progression of Prostate Cancer

Jody A. Charnow

OncologyNurseAdvisor

CANCER TYPES HOT TOPICS REGIMENS RESOU

NEWS CE FACT SHEETS PUBLISHERS ALLIA

August 26, 2021

Exercise Improves Cardiovascular Health of Men with Prostate Cancer Under Active Surveillance

Jennifer Larson

Catch up to speed

- Web-search keywords
- Look up references to see how the authors got to this point…

Research has shown that exercise improves cardiorespiratory fitness, physical functioning, body composition, fatigue, and quality of life during and after radical prostate cancer treatments.[6] Moreover, aerobic exercise has been found to suppress the progression of prostate tumors and metastasis in animal models[7] and to enhance the biochemical outcomes of prostate cancer growth in humans.[8,9] Furthermore, higher levels of physical fitness and functioning during active surveillance may ease adverse effects and lead to better cancer-related outcomes after radical treatments.[10,11] To our knowledge, however, only 1 clinical trial has examined the feasibility of exercise in men on active surveillance, and no trial has investigated the efficacy of an isolated exercise intervention during active surveillance.[12] In this Exercise During Active Surveillance for Prostate Cancer (ERASE) trial,[13] we aimed to examine the effects of exercise on cardiorespiratory fitness and biochemical progression in men with prostate cancer who were undergoing active surveillance. We hypothesized that high-intensity interval training (HIIT) would generate substantial improvements in both health-related fitness and biochemical progression of prostate cancer in men on active surveillance compared with patients receiving usual care.

REFERENCES

1. Mahal BA, Butler S, Franco I, et al. Use of active surveillance or watchful waiting for low-risk prostate cancer and management trends across risk groups in the United States, 2010-2015. *JAMA*. 2019;321(7):704-706. doi:10.1001/jama.2018.19941

2. Hamdy FC, Donovan JL, Lane JA, et al; ProtecT Study Group. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375(15):1415-1424. doi:10.1056/NEJMoa1606220

3. Neal DE, Metcalfe C, Donovan JL, et al; ProtecT Study Group. Ten-year mortality, disease progression, and treatment-related side effects in men with localised prostate cancer from the ProtecT randomised controlled trial according to treatment received. *Eur Urol*. 2020;77(3):320-330. doi:10.1016/j.eururo.2019.10.030

4. Dragomir A, Cury FL, Aprikian AG. Active surveillance for low-risk prostate cancer compared with immediate treatment: a Canadian cost comparison. *CMAJ Open*. 2014;2(2):E60-E68. doi:10.9778/cmajo.20130037

5. Keegan KA, Dall'Era MA, Durbin-Johnson B, Evans CP. Active surveillance for prostate cancer compared with immediate treatment: an economic analysis. *Cancer*. 2012;118(14):3512-3518. doi:10.1002/cncr.26688

6. Bourke L, Smith D, Steed L, et al. Exercise for men with prostate cancer: a systematic review and meta-analysis. *Eur Urol*. 2016;69(4):693-703. doi:10.1016/j.eururo.2015.10.047

7. Jones LW, Antonelli J, Masko EM, et al. Exercise modulation of the host-tumor interaction in an orthotopic model of murine prostate cancer. J Appl Physiol (1985). 2012;113(2):263-272. 22604887 doi:10.1152/japplphysiol.01575.2011

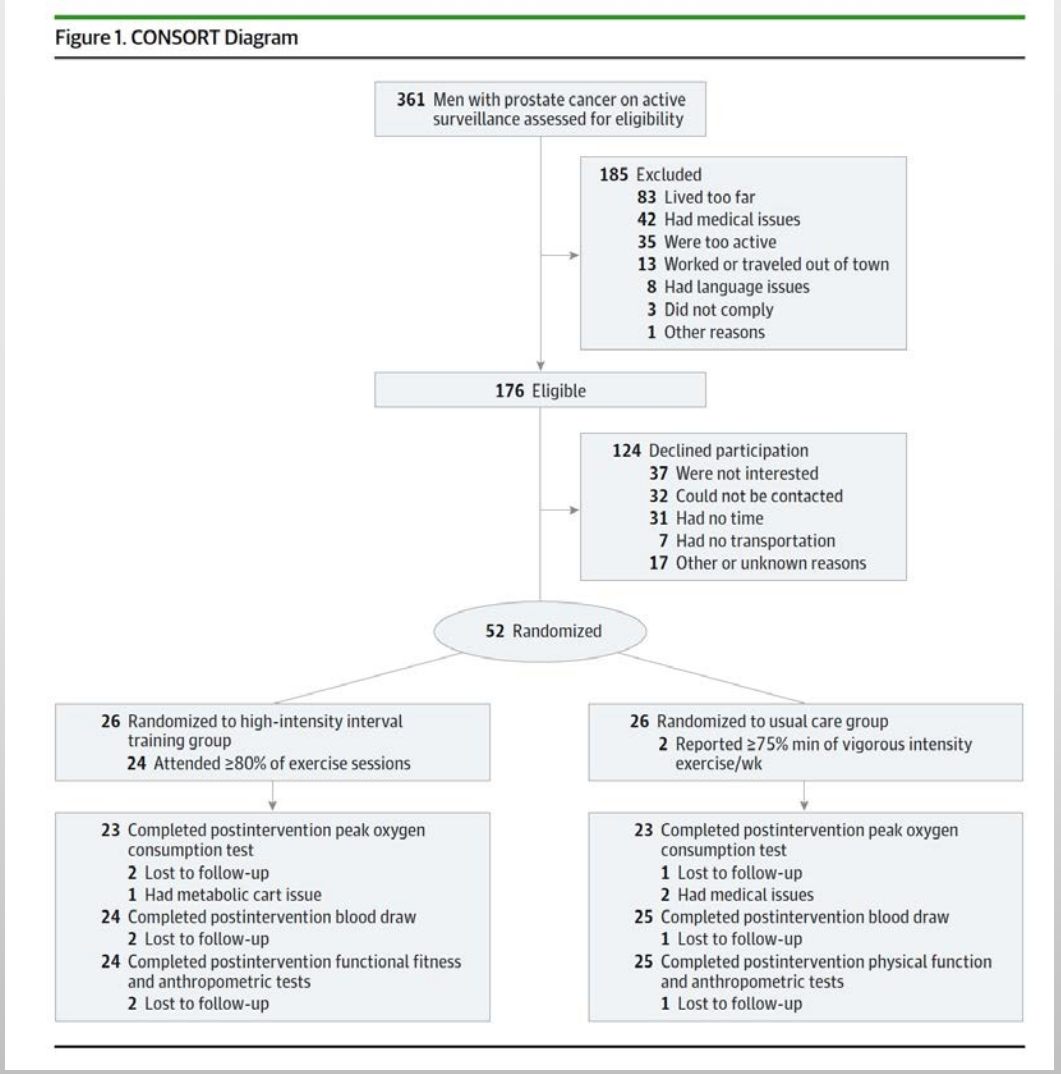
8. Rundqvist H, Augsten M, Strömberg A, et al. Effect of acute exercise on prostate cancer cell growth. *PLoS One*. 2013;8(7):e67579. doi:10.1371/journal.pone.0067579

9. Hvid T, Lindegaard B, Winding K, et al. Effect of a 2-year home-based endurance training intervention on physiological function and PSA doubling time in prostate cancer patients. *Cancer Causes Control*. 2016;27(2):165-174. doi:10.1007/s10552-015-0694-1

Materials and Methods

- Skim this section.
- When reading Results, may need to flip back to Methods section to clarify how experiments were done.
  - Sample number?
  - Conditions?
- You would read methods differently if needed to replicate the data or learn a new technique….**SURPRISE! Not as detailed as you thought!** (Can turn into a scavenger hunt of references.)

Methods
Figure 1 : Describes patient recruitment



Methods
Exercise program

Intervention

Participants who were randomized to the HIIT group were asked to complete a 12-week, thrice-weekly, supervised exercise program. The exercise program was individualized on the basis of each participant's baseline cardiopulmonary fitness, and the intensity and duration of exercise were increased over time. Each exercise session was performed on a treadmill and consisted of (1) a 5-minute warm-up at 60% of peak oxygen consumption ($\dot{V}O_2$), (2) an alternating 2-minute high-intensity interval at 85% to 95% of peak $\dot{V}O_2$ and a 2-minute active recovery at 40% of peak $\dot{V}O_2$, and (3) a 5-minute cooldown at 30% of peak $\dot{V}O_2$. Oxygen consumption was not directly measured during the exercise sessions, but the treadmill speed and grade were selected to match the targeted percentage of peak $\dot{V}O_2$ based on the baseline fitness levels. The number of high-intensity intervals was increased from 5 to 8 in each session, and the total duration of the exercise session was extended from 28 to 40 minutes.

Participants who were randomized to the usual care group were asked not to change their exercise levels during the intervention period. After the postintervention assessments at 12 weeks, the usual care group was offered a 4-week HIIT program at the center and/or referred to a 12-week community-based exercise program.

- Example: What was the HIIT (**H**igh-**I**ntensity **I**nterval **T**raining) exercise program?

Results

- Describes the **outcome** of experiments used to test hypothesis.
- Results often **simply stated** with *interpretation* coming later in the discussion. (*But sometimes combined in one section…)*
- **Figures and Tables** allow the reader to see the outcomes of the experiments for themselves!
- Don’t believe everything you read – be critical when looking at the data or experimental setup.
- **Subheadings** in the body of RESULTS often helps to outline the experiments and sometimes the conclusions.
- **Quick look?** *Skim the titles of the Figure Legends & text Subheadings to get a taste of the paper..*

Table 1

- Describes patient clinical data
  - Be critical…..Table addresses unintended factors that could skew the data (i.e. age, race, education, medical history)

Table 1. Baseline Characteristics of Participants

Variable	Overall (N = 52)	HIIT group (n = 26)	Usual care group (n = 26)
Exercise behavior, mean (SD)			
Vigorous aerobic exercise, min/wk	0	0	0
Moderate aerobic exercise, min/wk	61 (99)	59 (74)	62 (120)
Resistance exercise, min/wk	31 (54)	18 (42)	44 (62)

Exercise behavior has a high standard deviation (SD)

Table 1. Baseline Characteristics of Participants

Variable	Overall (N = 52)	HIIT group (n = 26)	Usual care group (n = 26)
Sociodemographic profile			
Age, mean (SD), y	63.4 (7.1)	63.9 (7.5)	62.8 (6.9)
White race, No. (%)	46 (89)	25 (96)	21 (81)
Married status, No. (%)	37 (71)	17 (65)	20 (77)
Completed university or college, No. (%)	20 (39)	9 (35)	11 (42)
Employed status, No. (%)	32 (63)	12 (48)	20 (77)
Family income of>$100 000/y, No. (%)	21 (40)	9 (35)	12 (46)
Medical profile			
Weight, mean (SD), kg	89.1 (16.3)	89.3 (18.7)	88.8 (14.0)
BMI, mean (SD)	29.0 (4.7)	29.0 (5.7)	29.0 (3.5)
Waist circumference, mean (SD), cm	102.3 (13.4)	101.4 (14.4)	103.3 (12.6)
Waist-hip ratio, mean (SD)	0.99 (0.08)	0.98 (0.09)	1.01 (0.07)
No. of comorbidities, No. (%)			
0	9 (17)	4 (15)	5 (19)
1	14 (27)	7 (27)	7 (27)
2	16 (31)	8 (31)	8 (31)
≥3	13 (25)	7 (27)	6 (23)
Most common comorbidities, No. (%)			
Arthritis or arthralgia	31 (60)	16 (62)	15 (58)
Hypertension	16 (31)	8 (31)	8 (31)
Metabolic condition	9 (17)	4 (15)	5 (19)
Prostate cancer profile			
Clinical stage, No. (%)			
T1c	47 (90)	24 (92)	23 (89)
T2a	4 (8)	2 (8)	2 (8)
T2b	1 (2)	0	1 (4)
Gleason grade, No. (%)			
1 (3 + 3 = 6)	50 (96)	25 (96)	25 (96)
2 (3 + 4 = 7)	2 (4)	1 (4)	1 (4)
PSA level, mean (SD), µg/L	7.3 (3.2)	6.0 (2.3)	8.6 (3.5)
Prostate volume, mean (SD), cc	52.9 (21.5)	55.6 (24.8)	50.3 (17.6)
PSA density, mean (SD), $\mu g \cdot L^{-1} \cdot cc^{-1}$	0.13 (0.07)	0.11 (0.06)	0.16 (0.08)
Positive cores, mean (SD), %	21.6 (13.0)	22.9 (14.2)	18.3 (10.5)
Time on active surveillance, mean (SD), mo	23.0 (25.8)	26.7 (27.0)	19.4 (24.4)
Behavioral profile			

Standard Deviation

- **SD is a measure of how dispersed the data is in relation to the mean**.

Formula

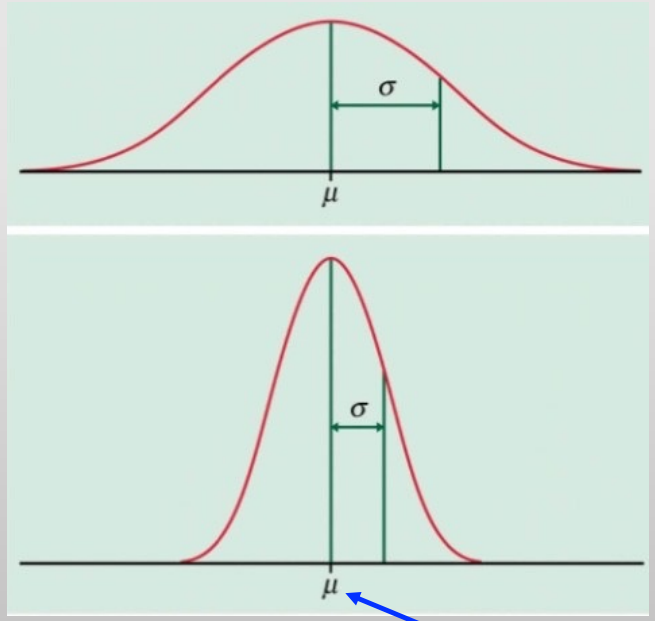
$$\sigma = \sqrt{\frac{\sum(x_i - \mu)^2}{N}}$$

σ = population standard deviation

N = the size of the population

x_i = each value from the population

μ = the population mean



Want a Low Standard Deviation. (means data are clustered around the mean.)

μ = mean of population

Table 2

- Data comparing HIIT vs Control
- Be critical.
- Is the data statistically significant?

***p*-value of <0.5 statistically significant**

Table 2. Effects of 12 Weeks of HIIT on Cardiorespiratory Fitness and Prostate Cancer–Related Biomarkers in Patients Under Active Surveillance

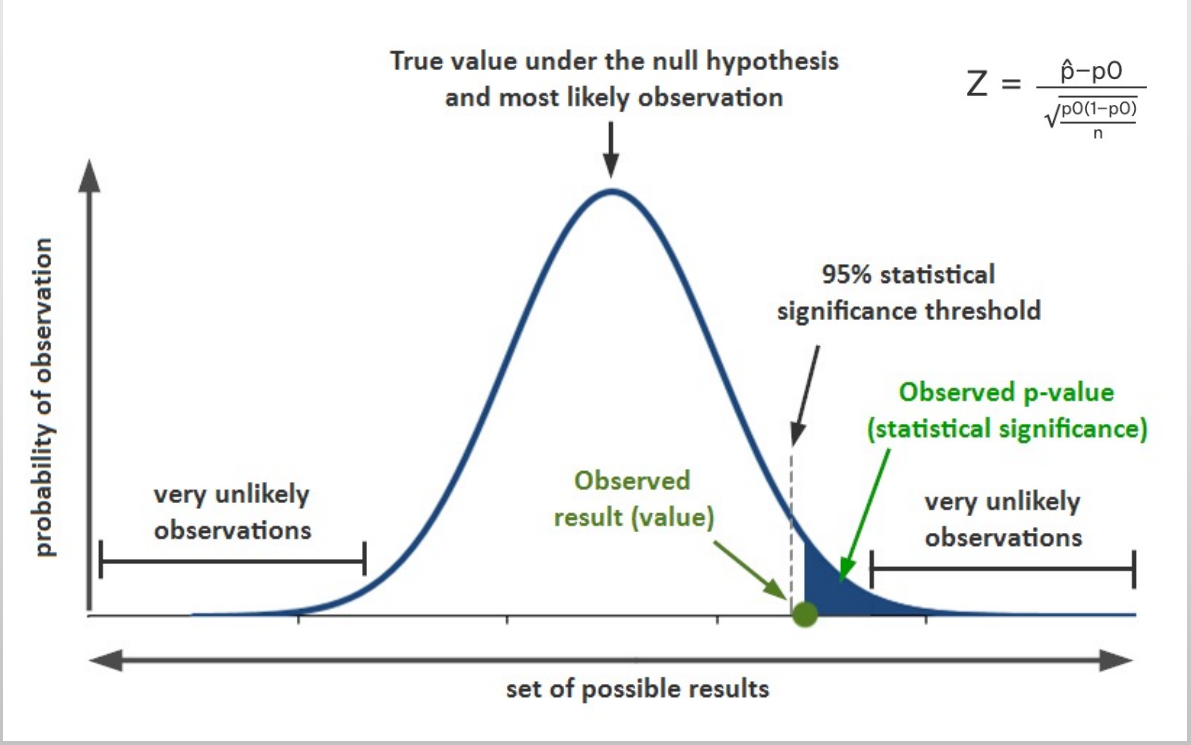
Variable	Mean (SD)		Mean (95% CI)		*P* value for adjusted between-group difference
	Baseline value	Postintervention value	Mean change	Adjusted between-group difference[a]	
Cardiopulmonary fitness					
Peak $\dot{V}o_2$, mL/kg/min					
HIIT group (n = 23)	29.6 (5.8)	30.4 (6.1)	0.9 (0.0 to 1.7)	1.6 (0.3 to 2.9)	.01
Usual care group (n = 23)	28.4 (6.9)	27.9 (7.0)	−0.5 (−1.4 to 0.4)		
Peak $\dot{V}o_2$, L/min					
HIIT group (n = 23)	2.55 (0.56)	2.60 (0.58)	0.05 (−0.01 to 0.12)	0.12 (0.00 to 0.20)	.03
Usual care group (n = 23)	2.51 (0.64)	2.46 (0.64)	−0.05 (−0.13 to 0.03		
Biochemical outcomes					
PSA level, µg/L					
HIIT group (n = 24)	6.1 (2.2)	5.7 (1.7)	−0.4 (−0.8 to 0.0)	−1.1 (−2.1 to 0.0)	.04
Usual care group (n = 25)	8.3 (3.2)	8.6 (4.2)	0.3 (−0.7 to 1.3)		
PSADT, mo					
HIIT group (n = 23)	61.3 (39.1)	80.2 (49.5)	18.9 (−1.2 to 38.9)	17.9 (−3.8 to 39.6)	.10
Usual care group (n = 24)	57.3 (37.6)	62.0 (36.5)	4.7 (−7.0 to 16.5)		
PSAV, µg/L/y					
HIIT group (n = 23)	1.1 (3.3)	0.1 (1.7)	−1.0 (−2.1 to 0.1)	−1.3 (−2.5 to −0.1)	.04
Usual care group (n = 24)	1.3 (5.0)	1.2 (5.2)	−0.1 (−1.0 to 0.8)		
Testosterone, nmol/L					
HIIT group (n = 22)	13.5 (4.6)	13.9 (3.9)	0.4 (−1.0 to 1.7)	1.0 (−0.7 to 2.6)	.24
Usual care group (n = 23)	12.1 (3.9)	12.0 (3.7)	−0.1 (−1.2 to 1.0)		
LNCaP proliferation, ODU					
HIIT group (n = 23)	0.23 (0.02)	0.21 (0.02)	−0.02 (−0.02 to −0.01)	−0.13 (−0.25 to −0.02)	.02
Usual care group (n = 24)	0.22 (0.03)	0.22 (0.03)	0.00 (−0.01 to 0.01)		

Abbreviations: HIIT, high-intensity interval training; ODU, optical density unit; PSA, prostate-specific antigen; PSADT, PSA doubling time; PSAV, PSA velocity; $\dot{V}o_2$, oxygen consumption.

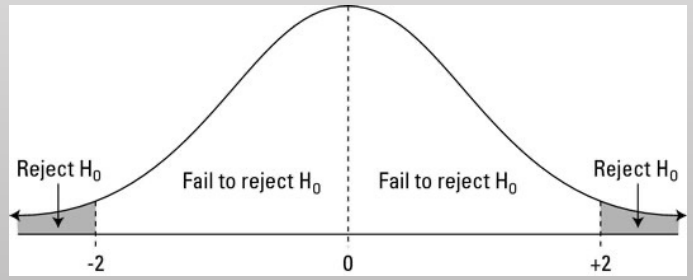
[a] Between-group difference was adjusted for the baseline values of the outcome and resistance exercise behavior.

P-Value

Used in Null Hypothesis Significance Testing (NHST) to decide whether to accept or reject a null hypothesis (which typically states that there is no underlying relationship between two variables)

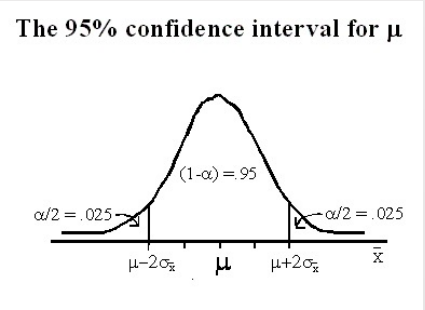


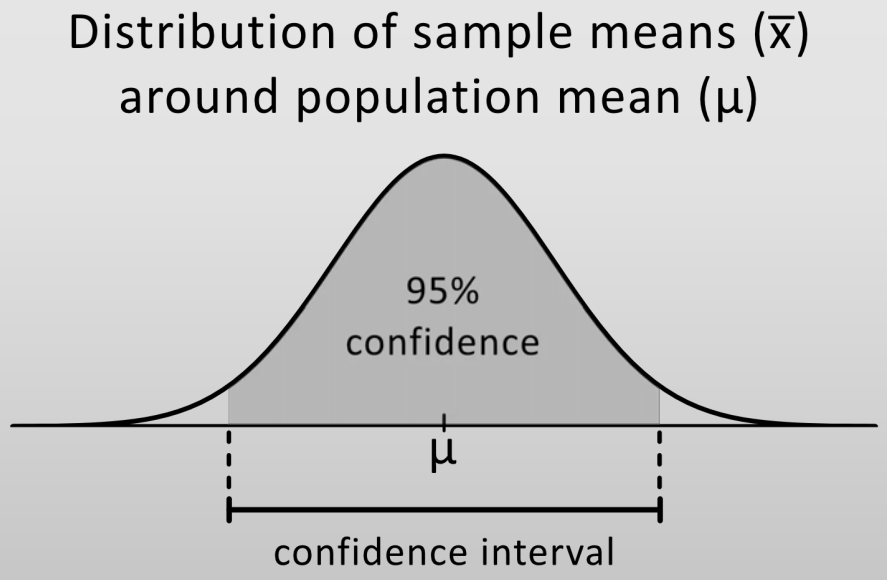
***If p*-value is <0.5**
the result
is considered statistically significant.
Null hypothesis is rejected.

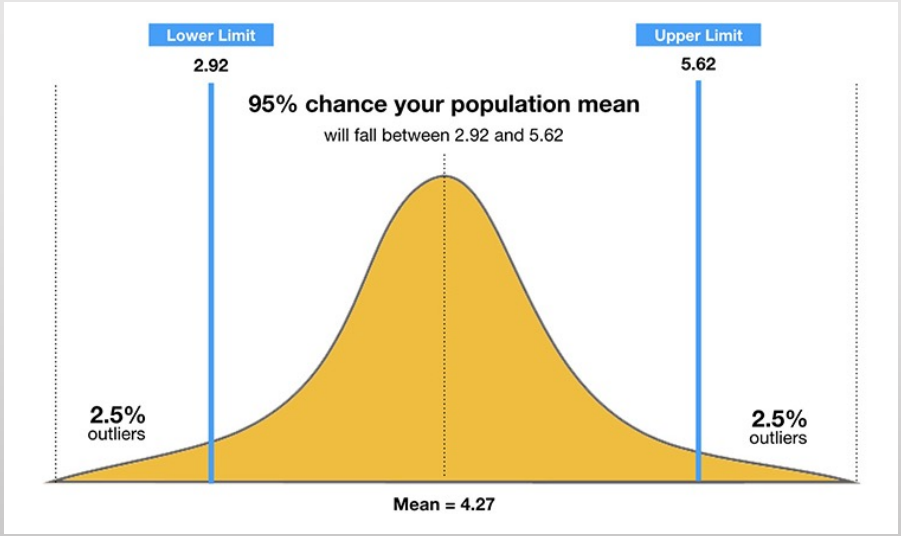


95% confidence interval

Range of values that you can be 95% confident contains the true mean of the population.







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HIIT group (n = 23)	0.23 (0.02)	0.21 (0.02)	−0.02 (−0.02 to −0.01)	−0.13 (−0.25 to −0.02)	.02
Usual care group (n = 24)	0.22 (0.03)	0.22 (0.03)	0.00 (−0.01 to 0.01)		

Abbreviations: HIIT, high-intensity interval training; ODU, optical density unit; PSA, prostate-specific antigen; PSADT, PSA doubling time; PSAV, PSA velocity; $\dot{V}O_2$, oxygen consumption.

[a] Between-group difference was adjusted for the baseline values of the outcome and resistance exercise behavior.

High SD so a bit uneasy of the "mean change" and adjusted group differences….

No change in androgen levels so what is regulating cell growth?

Changes in proliferation are small

Visual Abstract – best addition ever!

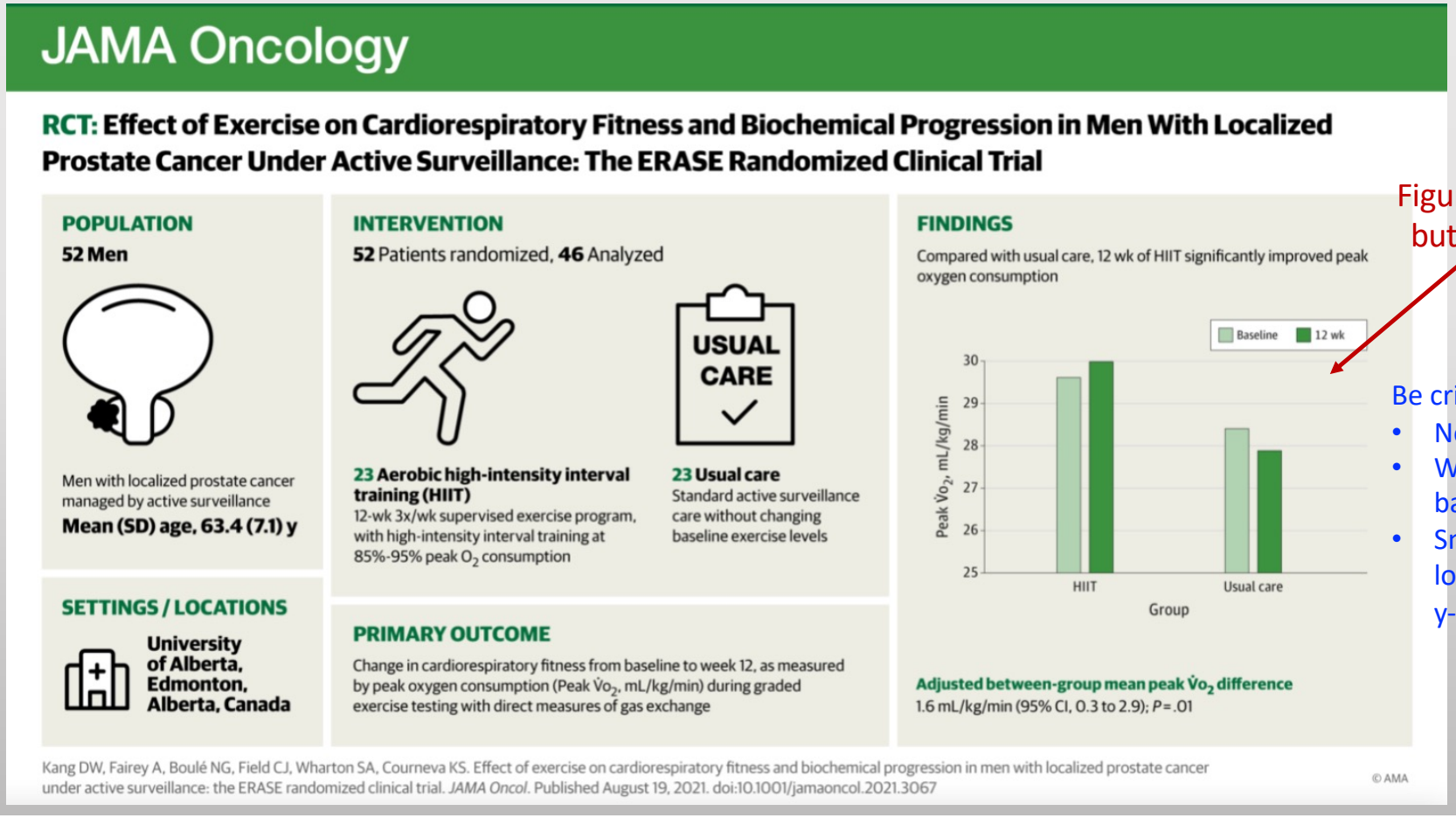


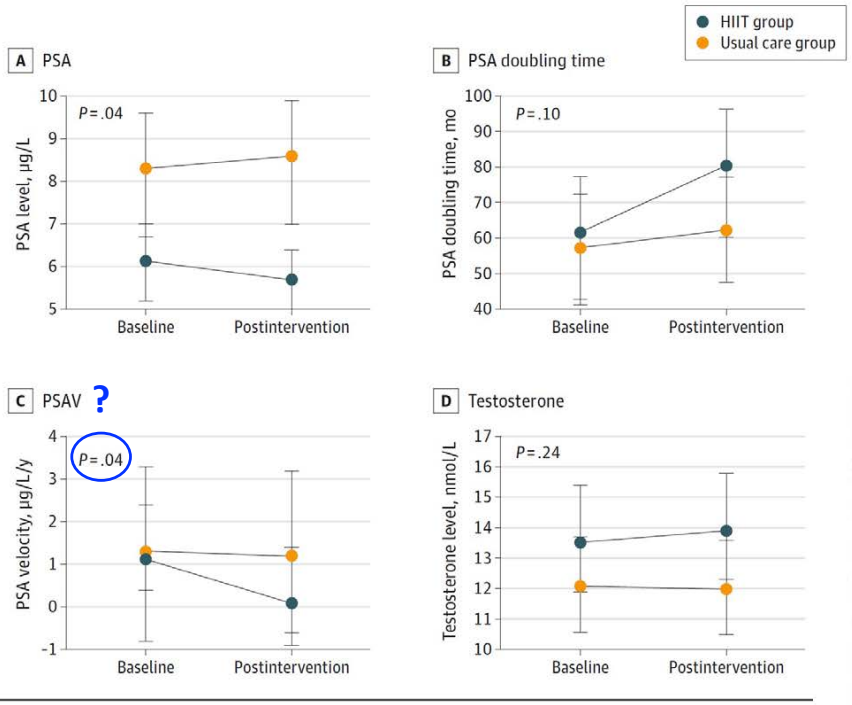
Figure not in paper but based on the data!

Be critical

- No error bars
- Why different baselines?
- Small differences look large on small y-axis scale….

Unadjusted data for PSA and Testosterone Values

Figure 2. Changes in Prostate-Specific Antigen (PSA), PSA Doubling Time, PSA Velocity, and Testosterone



Means are based on unadjusted data. Error bars indicate 95% CIs, and *P* values indicate between-group difference at the postintervention period adjusted for the baseline values of the outcome and resistance exercise behavior. HIIT indicates high-intensity interval training; PSAV, PSA velocity.

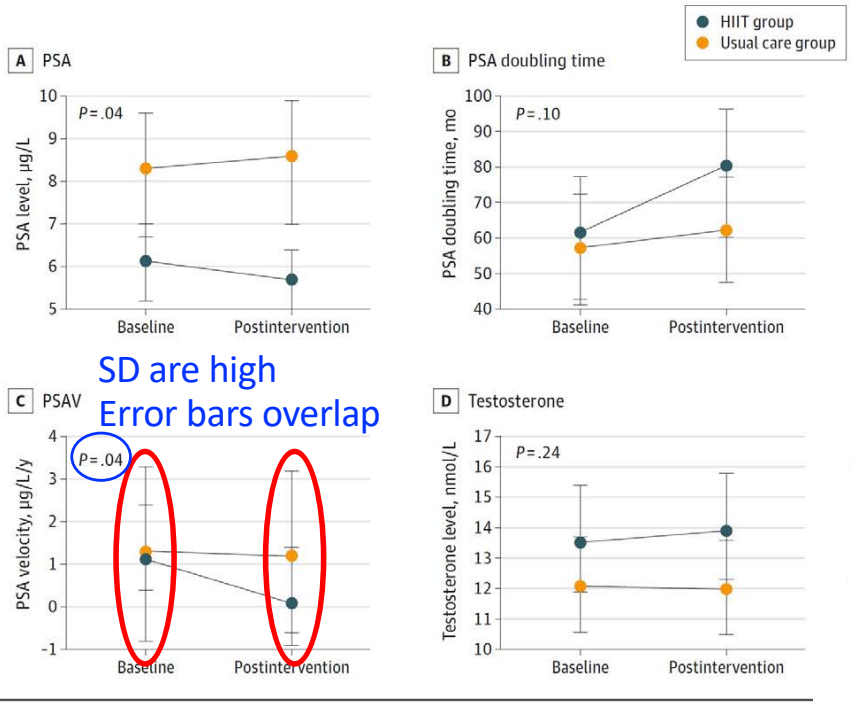
Terms

- PSAV (PSA velocity) - change over time, 3 measurement over 18-24m) (µg/L/yr).
- PSA doubling time – rate of rise in levels over time (mo).

- Be critical.
- Note that the P-values shown are not for the raw data but for the "between group differences". This is unconventional.
- P-values for PSAV raw data likely not significant due to high Standard Deviations…

“Unadjusted data” for PSA and Testosterone Values

Figure 2. Changes in Prostate-Specific Antigen (PSA), PSA Doubling Time, PSA Velocity, and Testosterone



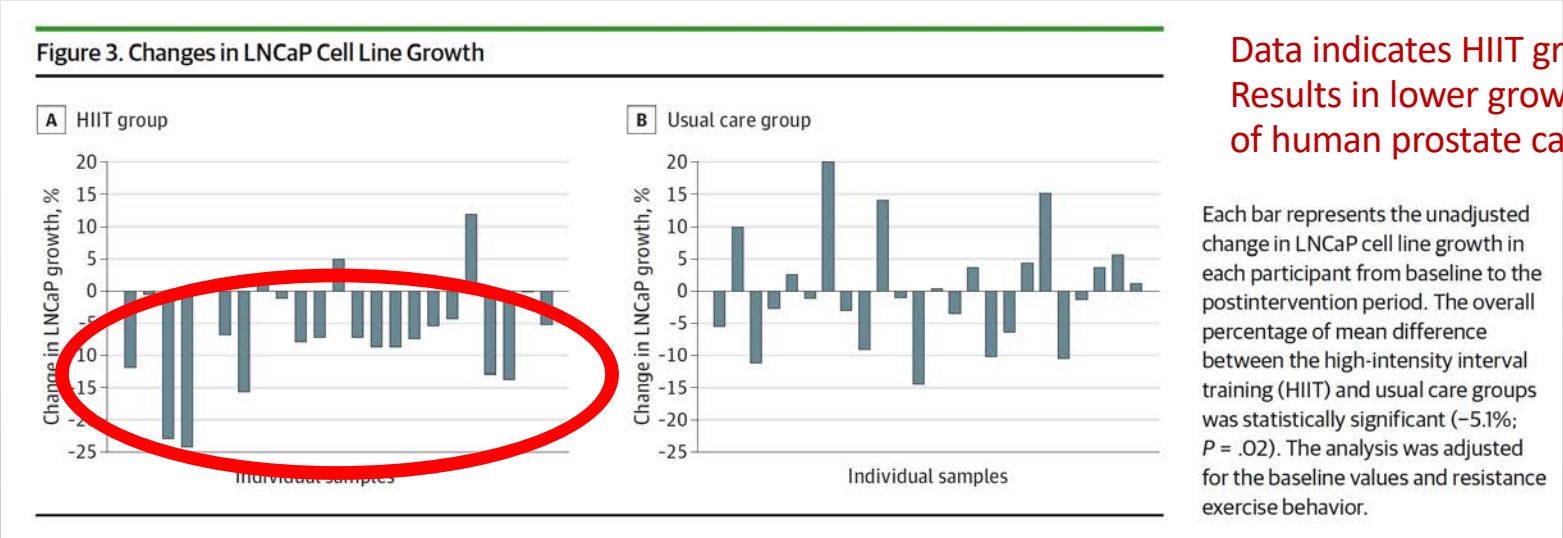
SD are high
Error bars overlap

Means are based on unadjusted data. Error bars indicate 95% CIs, and *P* values indicate between-group difference at the postintervention period adjusted for the baseline values of the outcome and resistance exercise behavior. HIIT indicates high-intensity interval training; PSAV, PSA velocity.

- Be critical.
- Note that the P-values shown are not for the raw data but for the “between group differences”. This is unconventional.
- P-values for PSAV raw data likely not significant due to high Standard Deviations…

Cell culture assay to determine impact of exercise on cell growth.

Never heard of this before. How was it done?

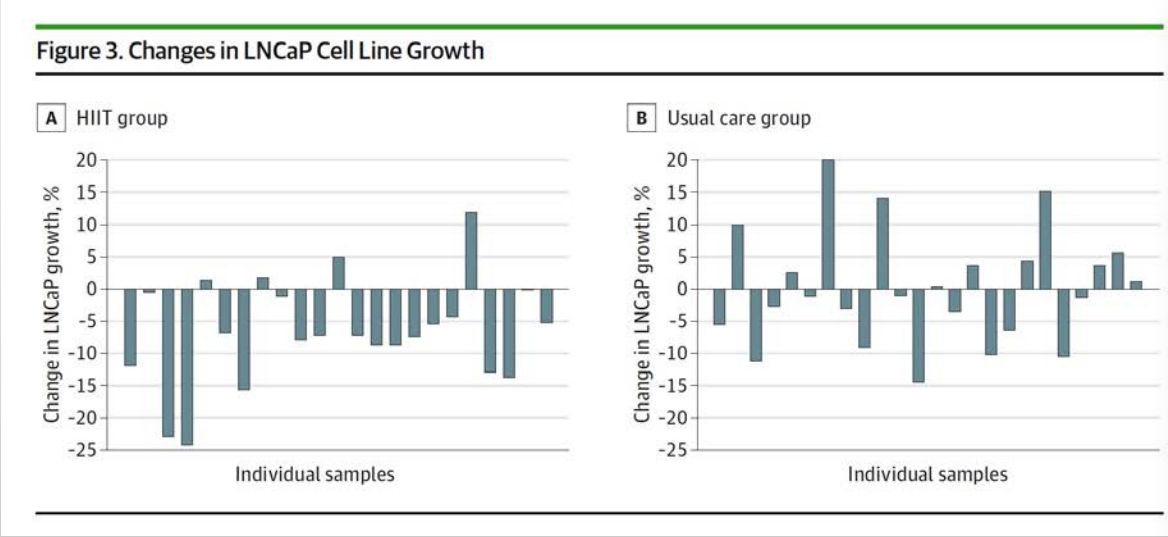


Data indicates HIIT group
Results in lower growth
of human prostate cancer cells

Each bar represents the unadjusted change in LNCaP cell line growth in each participant from baseline to the postintervention period. The overall percentage of mean difference between the high-intensity interval training (HIIT) and usual care groups was statistically significant (−5.1%; $P = .02$). The analysis was adjusted for the baseline values and resistance exercise behavior.

Cell culture assay to determine impact of exercise on cell growth.

How? Refer back to Methods Section



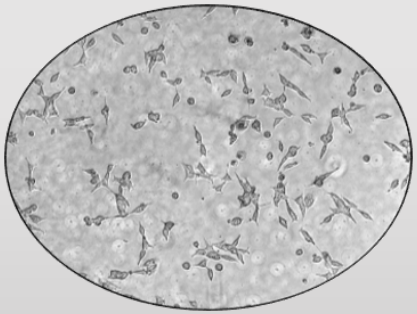
In addition to PSA levels and PSA kinetics, the effect of exercise on the proliferation of plasma prostate cancer cell line LNCaP was examined. LNCaP cell line was grown in ATCC-formulated RPMI 1640 medium (ATCC) and was supplemented with 5% FCS (fetal calf serum) and 1% penicillin-streptomycin. To determine cell proliferation, we seeded LNCaP cells (100 µL) at a concentration of 50 000 mL in a 96-well plate that contained either 5% FCS or 5% human plasma from test participants in triplicate for 48 hours. All samples were tested using the LNCaP cells at the same phase of growth. To determine final cell numbers, we removed supernatant and fixed the LNCaP cells with 100 µL of 4% paraformaldehyde in the plate for 20 minutes. Fixed cells were then incubated for an additional 20 minutes with 100 µL of 2% crystal violet (Fisher Scientific) dye solution (0.1%, wt/vol, with ethanol 2%, vol/vol in 0.5 M Tris-C1, pH 7.80).[8] The stained cells were washed in tap water and then solubilized with a sodium dodecyl sulfate solution (0.1%, wt/vol, with ethanol 50%, vol/vol, in 0.5 M Tris-C1, pH 7.8; 100 µL/well) for 30 minutes. The crystal violet dye was released by the fixed cells into the supernatant, and the absorbance was measured by a spectrophotometer (Molecular Devices LLC) at 600 nm.

Cell culture assay to determine impact of exercise on cell growth.

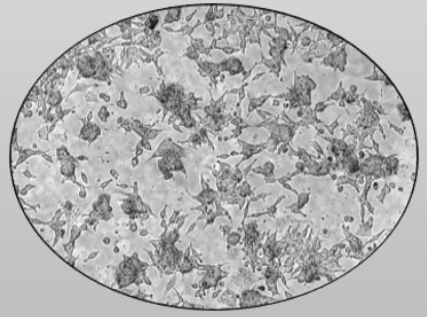
How? Refer back to Methods Section

LnCAP cells
Hormone Sensitive

Less purple



More purple



Grow cells 48 hrs with
- Media + 5% fetal calf serum
- Media + 5% patient plasma

↓

Stain cells with purple dye and measure color intensity

↓

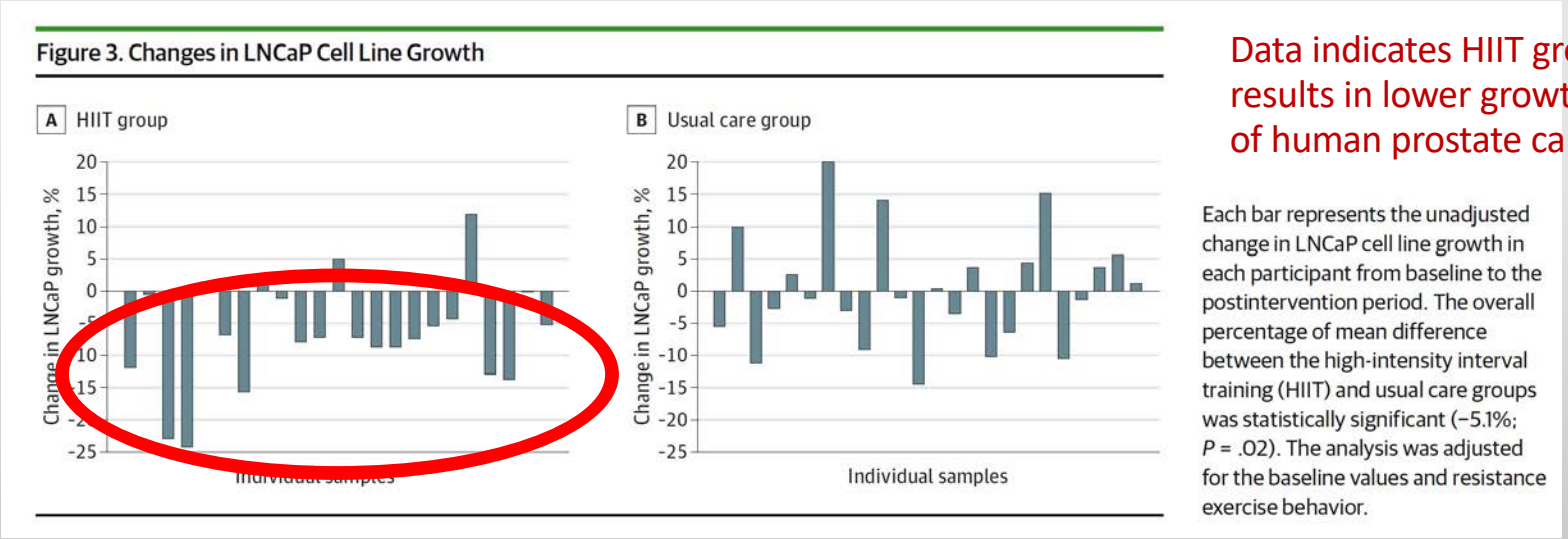
More purple = More cell growth

In addition to PSA levels and PSA kinetics, the effect of exercise on the proliferation of plasma prostate cancer cell line LNCaP was examined. LNCaP cell line was grown in ATCC-formulated RPMI 1640 medium (ATCC) and was supplemented with 5% FCS (fetal calf serum) and 1% penicillin-streptomycin. To determine cell proliferation, we seeded LNCaP cells (100 µL) at a concentration of 50 000 mL in a 96-well plate that contained either 5% FCS or 5% human plasma from test participants in triplicate for 48 hours. All samples were tested using the LNCaP cells at the same phase of growth. To determine final cell numbers, we removed supernatant and fixed the LNCaP cells with 100 µL of 4% paraformaldehyde in the plate for 20 minutes. Fixed cells were then incubated for an additional 20 minutes with 100 µL of 2% crystal violet (Fisher Scientific) dye solution (0.1%, wt/vol, with ethanol 2%, vol/vol in 0.5 M Tris-Cl, pH 7.80).[8] The stained cells were washed in tap water and then solubilized with a sodium dodecyl sulfate solution (0.1%, wt/vol, with ethanol 50%, vol/vol, in 0.5 M Tris-Cl, pH 7.8; 100 µL/well) for 30 minutes. The crystal violet dye was released by the fixed cells into the supernatant, and the absorbance was measured by a spectrophotometer (Molecular Devices LLC) at 600 nm.

Cell culture assay to determine impact of exercise on cell growth.

Be critical. How is this happening? Unknown…

It is NOT due to lower levels of androgen (testosterone) in patient plasma (Table 2)



Data indicates HIIT group results in lower growth of human prostate cancer cells

Each bar represents the unadjusted change in LNCaP cell line growth in each participant from baseline to the postintervention period. The overall percentage of mean difference between the high-intensity interval training (HIIT) and usual care groups was statistically significant (−5.1%; *P* = .02). The analysis was adjusted for the baseline values and resistance exercise behavior.

Table 2: Standard deviation of data is high so not sure if raw P-Values would be statistically significant….

Table 2

- Data comparing HIIT vs Control

_p_-value of <0.5 statistically significant

Table 2. Effects of 12 Weeks of HIIT on Cardiorespiratory Fitness and Prostate Cancer–Related Biomarkers in Patients Under Active Surveillance

Variable	Mean (SD)		Mean (95% CI)		*P* value for adjusted between-group difference
	Baseline value	Postintervention value	Mean change	Adjusted between-group difference[a]	
Cardiopulmonary fitness					
Peak $\dot{V}O_2$, mL/kg/min					
HIIT group (n = 23)	29.6 (5.8)	30.4 (6.1)	0.9 (0.0 to 1.7)	1.6 (0.3 to 2.9)	.01
Usual care group (n = 23)	28.4 (6.9)	27.9 (7.0)	−0.5 (−1.4 to 0.4)		
Peak $\dot{V}O_2$, L/min					
HIIT group (n = 23)	2.55 (0.56)	2.60 (0.58)	0.05 (−0.01 to 0.12)	0.12 (0.00 to 0.20)	.03
Usual care group (n = 23)	2.51 (0.64)	2.46 (0.64)	−0.05 (−0.13 to 0.03		
Biochemical outcomes					
PSA level, µg/L					
HIIT group (n = 24)	6.1 (2.2)	5.7 (1.7)	−0.4 (−0.8 to 0.0)	−1.1 (−2.1 to 0.0)	.04
Usual care group (n = 25)	8.3 (3.2)	8.6 (4.2)	0.3 (−0.7 to 1.3)		
PSADT, mo					
HIIT group (n = 23)	61.3 (39.1)	80.2 (49.5)	18.9 (−1.2 to 38.9)	17.9 (−3.8 to 39.6)	.10
Usual care group (n = 24)	57.3 (37.6)	62.0 (36.5)	4.7 (−7.0 to 16.5)		
PSAV, µg/L/y					
HIIT group (n = 23)	1.1 (3.3)	0.1 (1.7)	−1.0 (−2.1 to 0.1)	−1.3 (−2.5 to −0.1)	.04
Usual care group (n = 24)	1.3 (5.0)	1.2 (5.2)	−0.1 (−1.0 to 0.8)		
Testosterone, nmol/L	No change in androgen levels so what is regulating cell growth?				
HIIT group (n = 22)	13.5 (4.6)	13.9 (3.9)	0.4 (−1.0 to 1.7)	1.0 (−0.7 to 2.6)	.24
Usual care group (n = 23)	12.1 (3.9)	12.0 (3.7)	−0.1 (−1.2 to 1.0)		
LNCaP proliferation, ODU	Changes in proliferation are small				
HIIT group (n = 23)	0.23 (0.02)	0.21 (0.02)	−0.02 (−0.02 to −0.01)	−0.13 (−0.25 to −0.02)	.02
Usual care group (n = 24)	0.22 (0.03)	0.22 (0.03)	0.00 (−0.01 to 0.01)		

Abbreviations: HIIT, high-intensity interval training; ODU, optical density unit; PSA, prostate-specific antigen; PSADT, PSA doubling time; PSAV, PSA velocity; $\dot{V}O_2$, oxygen consumption.

[a] Between-group difference was adjusted for the baseline values of the outcome and resistance exercise behavior.

Discussion

- Data is analyzed to show what the authors believe the data shows. (You don't have to agree with their interpretations!)
- Findings are related to other findings in the field (contribute to knowledge, correct errors, etc.)
- How is this work significant?
- List strengths and limitations/shortcomings of study, providing suggestions about areas that need additional research.
- This is the most important section of the article where the research questions are answered and the meaning of analysis and interpretation of the data are presented.

How to read a discussion

Take notes and answer these questions:

- What **conclusions** do the authors draw? Be sure to separate fact from their opinion/interpretation?
- Describe for yourself **why these data significant**. (Does it contribute to knowledge or correct errors?)

Discussion
Overall Conclusion

Discussion

To our knowledge, the ERASE trial was the first randomized clinical trial to examine the efficacy of HIIT in men with localized prostate cancer undergoing active surveillance. As we hypothesized, a supervised 12-week HIIT program significantly improved cardiorespiratory fitness and indicators of prostate cancer biochemical progression. These improvements appear to be meaningful and may translate into better outcomes for patients with prostate cancer who are being managed by active surveillance.

Conclusions

To our knowledge, the ERASE trial was the first to demonstrate that HIIT increases cardiorespiratory fitness and inhibits the biochemical progression of prostate cancer in men on active surveillance. To support the findings of this trial and to determine whether the improvements can translate into better long-term clinical outcomes, larger randomized clinical trials are warranted.

Conclusion
Authors Strengths & Weaknesses

Strengths and Limitations

This study has strengths. These strengths include the understudied cancer setting, the novel exercise intervention, the randomized clinical trial design, high adherence to the intervention, minimal loss to follow-up, and assessment of prostate cancer-related biochemical outcomes.

This study also has limitations. These limitations include potentially low statistical power due to failure to achieve the target sample size (87%), some missing data (6%-12%), and a shortened intervention period for 3 participants. Additional limitations are the potential recruitment bias (eg, more fit and active men), unblinded outcome assessors for the primary outcome, and lack of long-term follow-up for clinical outcomes.

Strengths:

- Novel: AS group – Phase 2 randomized efficacy study to link exercise intervention and biochemical outcomes.

Limitations:

- Smaller recruitment than expected.
- Lack of long-term follow-up for clinical outcome (No data to say exercise impacted cancer progression in patients…just cells in a petri dish!)

Discussion
Conflicting Data

We observed inhibitory effects of HIIT on the biochemical progression of prostate cancer. The decreased PSA level in this trial is in contrast to findings in most exercise trials among patients with prostate cancer who reported no significant changes in PSA level.[26-32] This discrepancy may be attributed to patients in previous studies undergoing androgen deprivation therapy and/or radiation therapy, which can substantially lower PSA levels. One exploratory exercise study that was conducted in patients with prostate cancer on active surveillance reported no changes in PSA concentration after a yearlong, home-based exercise intervention.[12] In comparison, the exercise program in the present study focused on high-intensity aerobic training (ie, 85%-95%) for a shorter-term (ie, 12 weeks), which can exert greater physiological changes (eg, sympathetic activation and mobilization of cytotoxic immune cells).[33,34] The data suggest that high-intensity aerobic exercise might be necessary to produce changes in biochemical outcomes in prostate cancer.

Findings here don't match other groups

- Cited 7 papers showing PSA in PCa patients don't change with exercise.
  - Past studies: PCa patients undergoing androgen-deprivation or radiation therapies…
  - Cited 1 study in AS patients showing exercise after 1 yr cause no change in PSA!
- **Not matching past data doesn't make it a bad study!** Perhaps this novel high-intensity aerobic training causes distinct biological effects (ie, immune response)? MORE STUDIES NEEDED

Discussion Interpretation/Caution

Both PSAV and PSADT are associated with prostate cancer progression and mortality, independent of PSA.[35,36] A PSAV that is greater than 0.75 µg/L/y has been used as a criterion of progression to radical treatment in active surveillance settings,[37] and the change in PSAV in this trial of −1.3 µg/L/y may be clinically meaningful. Similarly, we found a nonsignificant but meaningful between-group difference in PSADT of 17.9 months. Previous studies have shown that higher fitness levels are associated with longer PSADT in patients with prostate cancer, which suggests that HIIT may have the potential to delay the progression of prostate cancer.[9] However, PSA kinetics have been examined mostly in patients with advanced prostate cancer[38] and are still under investigation in the active surveillance setting.[39] Therefore, caution is required when interpreting PSA kinetics in patient cohorts under active surveillance.

Interpretation:

- **The Good:** HIIT Program decrease in PSAV may be clinically meaningful!
- **The Bad:** Authors try to link a non-significant PSADT finding to clinical outcome?
- **The Reality:** More work/ bigger clinical trial is warranted.

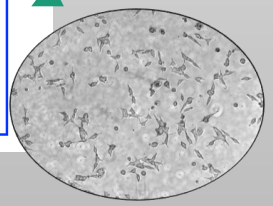
Results align with other data

Furthermore, HIIT suppressed the proliferation of LNCaP cells by 5.1%, compared with usual care, suggesting that HIIT may have played an inhibitory role in prostate cancer cell growth in this setting. This finding is consistent with results of a study by Rundqvist et al,[8] which showed a 31% inhibition of LNCaP cell proliferation in postexercise serum when compared with rest in healthy men. A few lifestyle trials have also suggested the inhibitory effects of combined exercise and diet interventions on LNCaP cell growth by 30% to 44% in healthy men[40] and by 70% in men with prostate cancer on active surveillance.[41] We believe the ERASE trial was the first to show the suppressive effects of exercise alone on LNCaP along with decreased PSA levels and PSAV.

Mechanism? No data = Handwaving

The biological mechanisms of the effects of exercise on prostate cancer are unclear. One plausible mechanism is the enhanced immunosurveillance after exercise training or even during a single bout of exercise.[42,43] Specifically, exercise can mobilize cytotoxic natural killer cells into circulating blood and can redistribute these cells into tumor cells with assistance from the exercise-induced increases in circulating norepinephrine and IL-6[34]; this process appears to require endurance exercise at high intensity.[9,42] Other possible explanations include that exercise could suppress prostate cancer progression by modulating systemic inflammatory mediators,[44] metabolic biomarkers,[8] and tumor vascularization and perfusion.[45] More research in active surveillance clinical settings is necessary to identify the biophysiological associations between exercise and prostate cancer[46] and to further explore potential tumor-related biomarkers.[47]

Decreased growth of LNCaP human prostate cancer cells using post-exercise patient blood aligns with past data.
So what is new????



Discussion
Impact and future steps

Given that no statistical adjustment for multiple testing on the PSA-related secondary outcomes was made, confirmatory studies are needed to support the findings in this trial. Larger randomized clinical trials are warranted to determine whether improvements in cardiorespiratory fitness and prostate cancer–related markers translate into better long-term clinical outcomes in men with prostate cancer on active surveillance.[48]

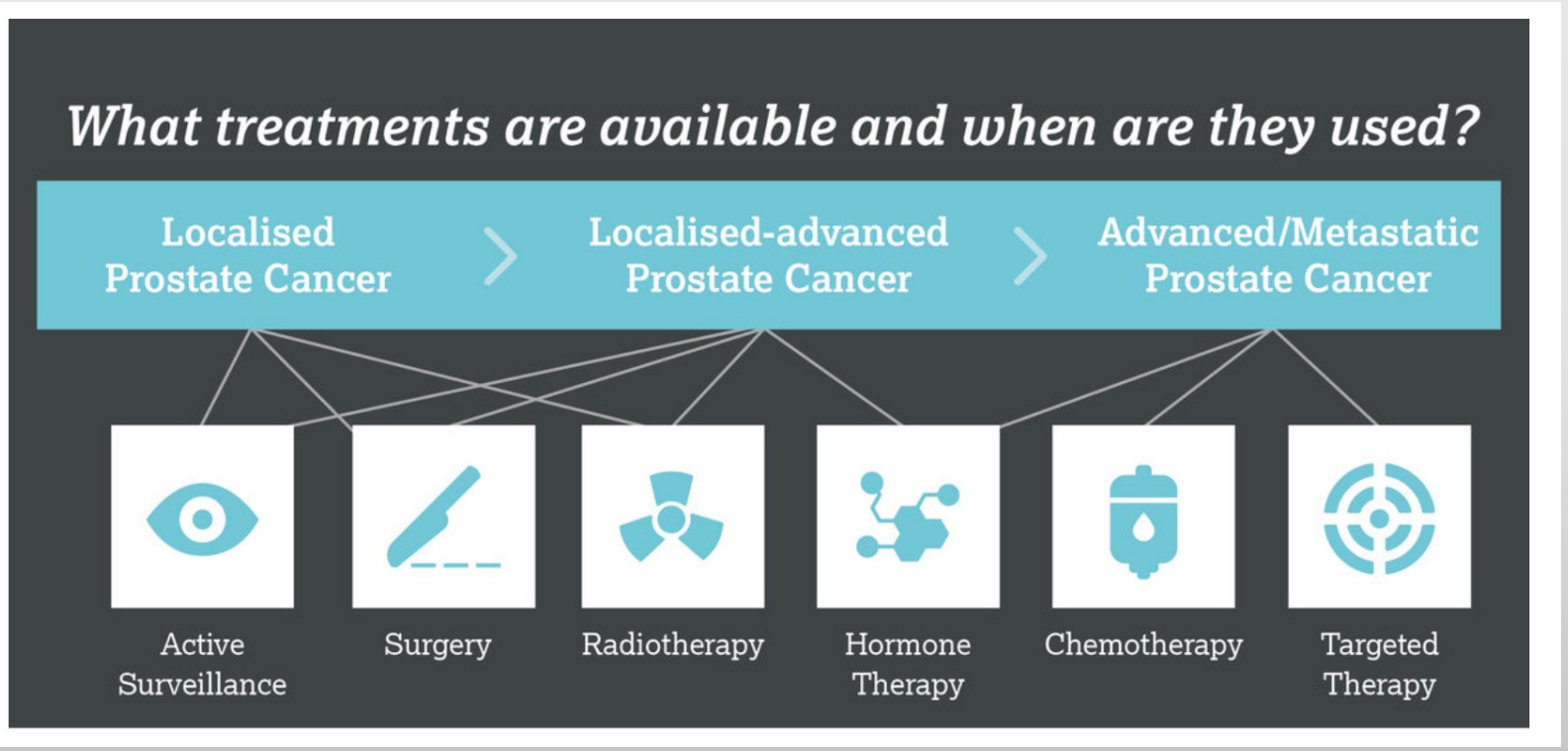
Evaluating a Paper – What do YOU think?

- What is the problem being solved?
  - Is it important? Relevant? Why?
  - What is the prior work in this area?
- Is the proposed solution novel?
- Are the assumptions and model backed by strong data?
- Impact
  - Easier to evaluate for older papers
  - Does other work build on it? Do other papers uses techniques and solutions proposed in this paper?

Evaluation Process

- Read slowly, take notes as you read
  - Question assumptions, importance of the problem
  - Write questions to track what you don't understand
- Sometimes what is not in the paper is more important than what is in it!
  - Is there something the authors have overlooked?
- Don't let ideas or design details pass until you understand them!
- Do not assume the paper is correct, even if published in a prestigious peer-reviewed venue

Prostate Cancer Therapies



Immunotherapy (Provenge, PD-1 inhibitors)

Proton beam
CRT
IMRT
Brachytherapy

abiraterone (Zytiga)
enzalutamide (Xtandi)
apalutamide (Erleada)

docetaxel (Taxotere)
cabazitaxel (Jevtana)

PARP inhibitors
Monoclonal Abs

Table 3

Advantages and Disadvantages of Treatment Modalities for Localized Prostate Cancer

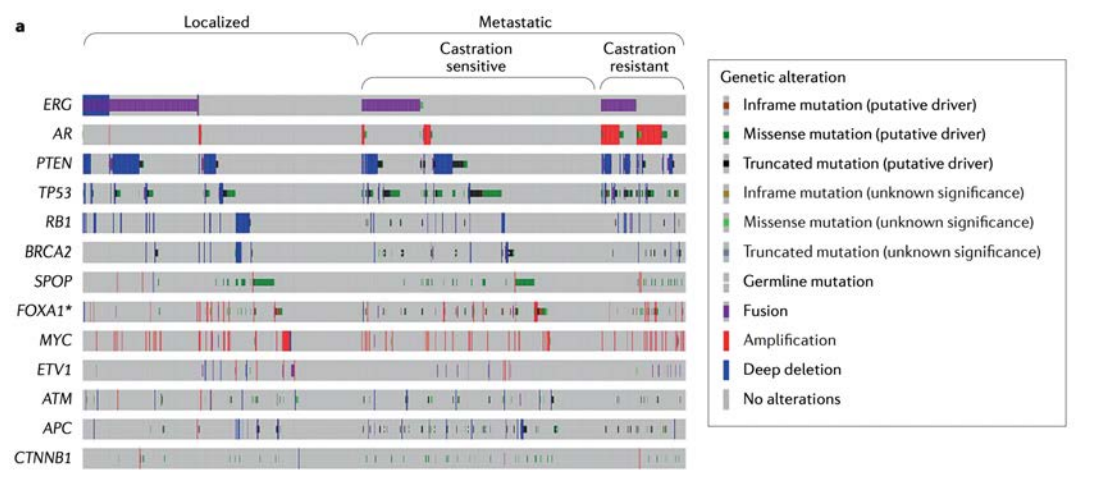
Treatment Modality	Advantage	Disadvantage
External beam radiation	• Lower risk of urinary incontinence and bleeding • Option for nonsurgical candidates, elderly, and those with significant comorbidities	• High risk of erectile dysfunction • Long treatment course (8-9 wk) • Bladder or bowel symptoms during treatment are common
Brachytherapy	• Control rates comparable to surgery for low-risk tumor • Can be used alone or as a "boost" • Single treatment	• High risk of erectile dysfunction • Bladder or bowel symptoms during treatment are common • General anesthesia is required
Radical prostatectomy	• Definitive curative therapy for prostate-confined disease • Easy to detect PSA failure	• High risk of erectile dysfunction • Risk of long-term incontinence • Risk of operative morbidity
Active surveillance	• Avoids or delays treatment-associated morbidity • Allows quality of life to be maintained • Prevents overtreatment	• Risk of progression past possibility of cure • Frequent monitoring and physician visits • Increased anxiety

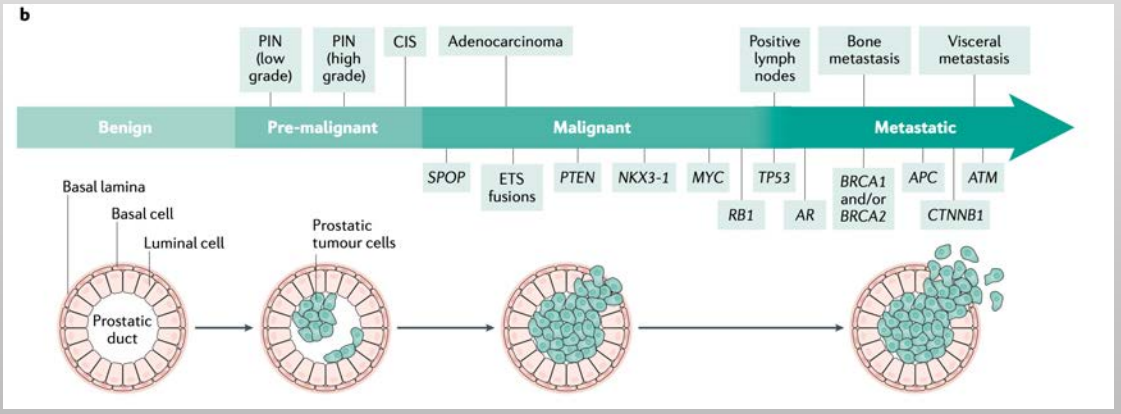
Source: References 4, 12, 14.

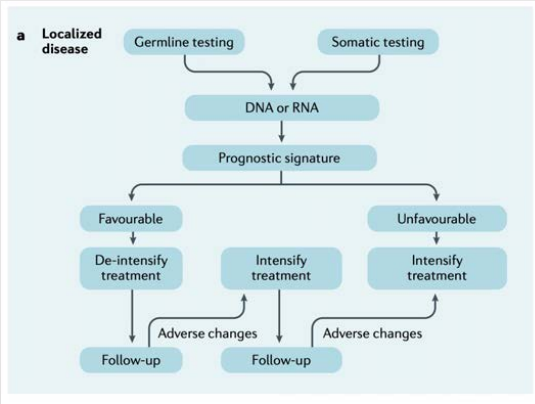
Genetic alterations in prostate cancer

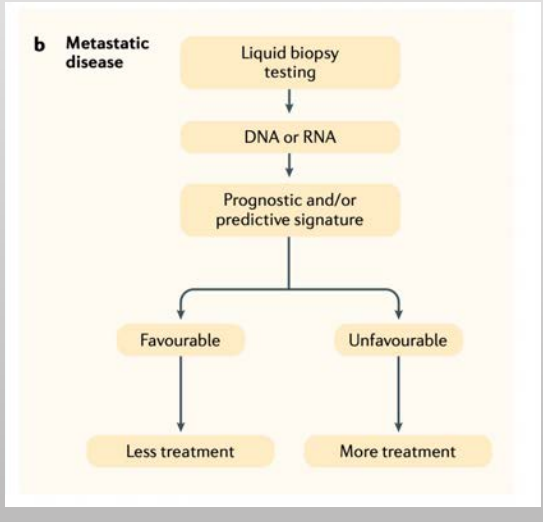
biomarkers/therapeutic targets

Screening (PCA3, 4Kscore, TMPRSS2:ERG, ExoDx)









FDA Approval 12/20: Prostate cancer imaging

U.S. FOOD & DRUG ADMINISTRATION

Home / News & Events / FDA Newsroom / Press Announcements / FDA Approves First PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer

FDA NEWS RELEASE

FDA Approves First PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer

December 01, 2020

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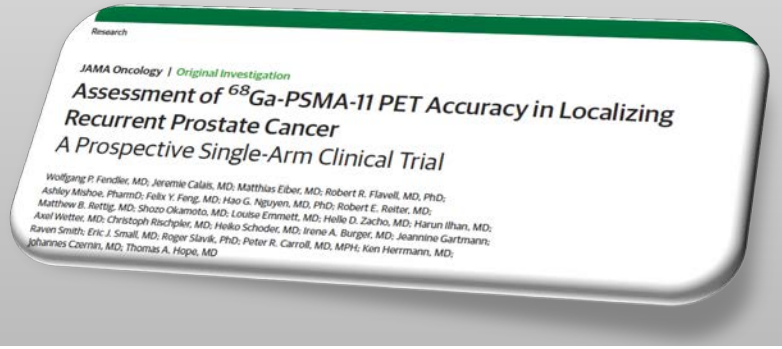
For Immediate Release: December 01, 2020

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-018-4189-7

ORIGINAL ARTICLE

^{68}Ga-PSMA-11 PET/CT in recurrent prostate cancer: efficacy in different clinical stages of PSA failure after radical therapy

Francesco Ceci[1,2,3] · Paolo Castellucci[1] · Tiziano Graziani[1] · Andrea Farolfi[1] · Cristina Fonti[1] · Filippo Lodi[1] · Stefano Fanti[1]



Research

JAMA Oncology | Original Investigation

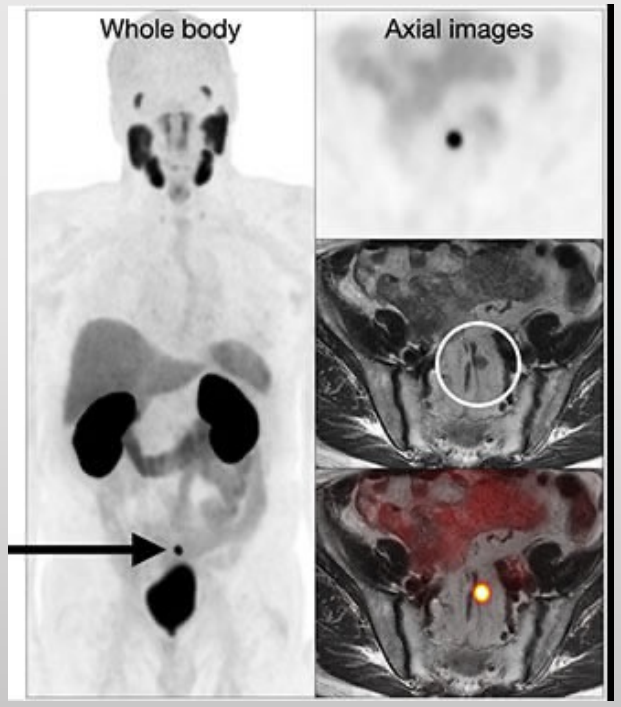
Assessment of ^{68}Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer

A Prospective Single-Arm Clinical Trial

Wolfgang P. Fendler, MD; Jeremie Calais, MD; Matthias Eiber, MD; Robert R. Flavell, MD, PhD; Ashley Mishoe, PharmD; Felix Y. Feng, MD; Hao G. Nguyen, MD, PhD; Robert E. Reiter, MD; Matthew B. Rettig, MD; Shozo Okamoto, MD; Louise Emmett, MD; Helle D. Zacho, MD; Harun Ilhan, MD; Axel Wetter, MD; Christoph Rischpler, MD; Heiko Schoder, MD; Irene A. Burger, MD; Jeannine Gartmann; Raven Smith; Eric J. Small, MD; Roger Slavik, PhD; Peter R. Carroll, MD, MPH; Ken Herrmann, MD; Johannes Czernin, MD; Thomas A. Hope, MD

Prostate cancer imaging

^{68}Ga-PSMA ligands – great promise in early detection of aggressive disease/BR



PET Tracer	Target	Benefit for Prostate Cancer	Role in Prostate Cancer Imaging
FDG	Glucose metabolism	None or limited	Response assessment of osseous disease in metastatic castration-resistant prostate cancer; prognostic indicator
^{11}C-Choline or ^{18}F-choline	Cell membrane metabolism	Yes, in large studies	High-risk staging; biochemical relapse at high PSA levels
^{68}Ga-PSMA ligands	PSMA	Yes, in large studies	Biochemical relapse at low PSA levels
^{18}F–Sodium fluoride	Osteoblastic activity	Bone metastases only	Bone metastases only
^{18}F-Fluciclovine	Amino acids	Yes, in initial results	Undergoing evaluation but appears superior to choline in the setting of biochemical relapse

Prostate cancer imaging

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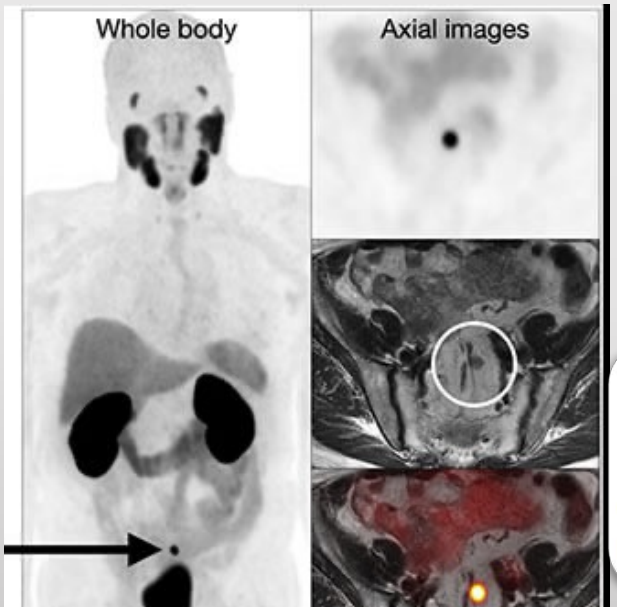

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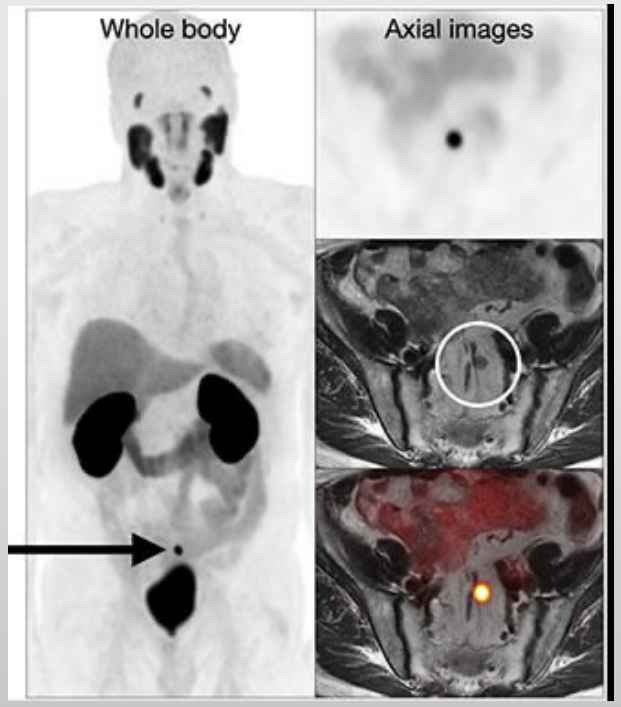
Table 5 Comparison of ^{68}Ga-PSMA-11 PET/CT results with choline PET/CT, pelvic mp-MRI, and bone scintigraphy

	Choline PET/CT (137)		Pelvic mp-MRI (78)		Bone scintigraphy (45)	
	Choline +	Choline −	mp-MRI +	mp-MRI −	Bone scan +	Bone scan −
PSMA +	11	73	6	32	5	20
PSMA −	2	51	3	37	0	20

Results in literature suggest a superior detection rate of ^{68}Ga-PSMA-11 PET/CT over other techniques, including choline-based and fluciclovine-based PET/CT imaging [23, 28]. Our study confirms these results: in our patient series, when ^{68}Ga-PSMA-11 PET/CT was positive, correlative imaging resulted negative in 83% of cases. In a few cases only, choline PET/CT or mp-MRI resulted positive while ^{68}Ga-PSMA-11 PET/CT resulted negative (1.5 and 3.8% of cases respectively).

Prostate cancer imaging

^{68}Ga-PSMA ligands – great promise in early detection of aggressive disease/BR



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

New targeted radioligand therapy (June 23, 2021)

CONCLUSIONS

Radioligand therapy with ^{177}Lu-PSMA-617 prolonged imaging-based progression-free survival and overall survival when added to standard care in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer. (Funded by Endocyte, a Novartis company; VISION ClinicalTrials.gov number, NCT03511664.)

Summary

- Step 1: Skim the entire paper
- Step 2: Vocabulary
- Step 3: Read for comprehension, section by section
- Step 4: Reflection and criticism

Thank you!

- Contact info: Aurora Esquela Kerscher <kerschae@evms.edu>

References Used on How to Read a Research Paper

- Drew Dennis https://medium.com/@drewdennis/how-to-read-scientific-papers-quickly-efficiently-e7030c4018fa
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