24-25 Marzo 2023
Ospedaletto di Pescantina (VR)
Centro Congressi Park Hotel Villa Quaranta

Microambiente e carcinoma mammario: dal significato biologico a target terapeutico?

Elia Biganzoli - Università Statale di Milano
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Francesca Bianchi, Daniela Lucini, Nicla La Verde
& Christine Desmedt, KU Leuven

DISCLOSURE

- Drug-Discovery and High Throughput Screening, Dow-Lepetit

- Senior Biostatistician - Fondazione IRCCS Istituto Nazionale dei Tumori, Milano
- Full Professor, Medical Statistics – University of Milano & DSRC

- Leader of Task force 5 Evaluation & Benchmarking EU FP6 NoE BIOPATTERN
  Computational Intelligence for BioPattern Analysis to Support eHealthcare

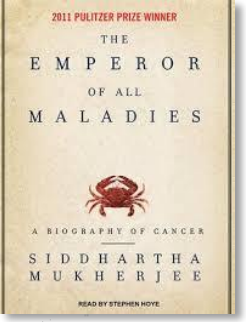
- Clinical Epidemiology consultant for the Italian Government, ILVA Taranto

- Collaboration agreement with Institute Jules Bordet, Bruxelles & KU Leuven

- Independent Scientific Advisor of the mHealth company MyMeleon Inc. Palo Alto CA, USA.

WEB OF SCIENCE™

Surgery paradigms and breast cancer dormancy



"In God we trust. All others must have data."

Bernard Fisher, MD, FACS – Surgeon and Cancer Pioneer

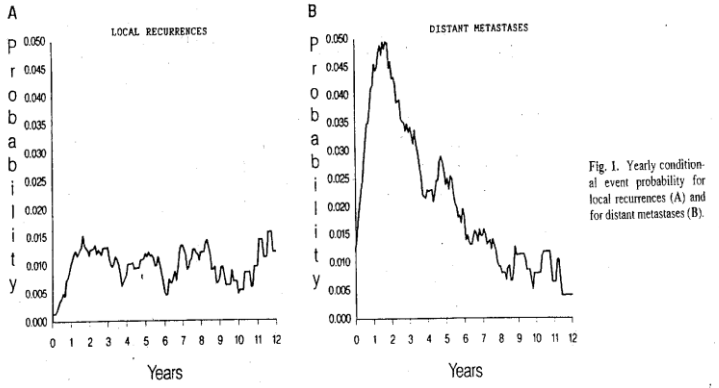


Fig. 1. Yearly conditional event probability for local recurrences (A) and for distant metastases (B).

Veronesi U. et al.; *J.Natl.Canc.Inst.,* 1995

The Breast 52 (2020) 64–70

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Late effects of adjuvant chemotherapy adumbrate dormancy complexity in breast cancer

Romano Demicheli [a,*], Christine Desmedt [b], Mike Retsky [c], Christos Sotiriou [d], Martine Piccart [e], Elia Biganzoli [a,**]

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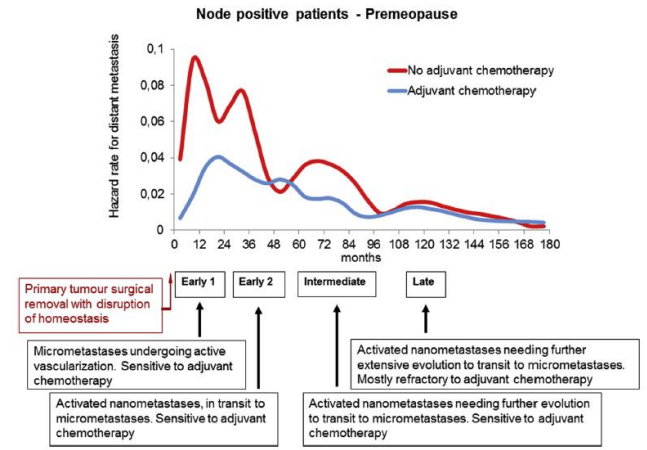
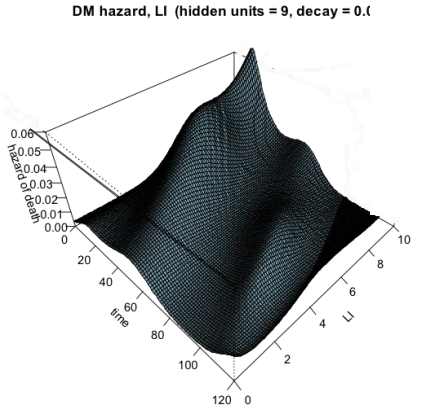


Fig. 4. Outline of the time extended model describing the metastatic process. Findings of present analysis are compatible with the presence of one micro-metastatic state (corresponding to the early-1 peak) and three different nano-metastatic states (corresponding to the early-2, intermediate and late peaks) that are under the effect of the homeostatic control from the primary tumour. Primary tumour removal disrupts the homeostasis and enhances transitions between dormancy states. If surgery induced transitions are chemo sensitive, the corresponding peaks will be dampened by adjuvant chemotherapy. On the base of such picture, the pattern of microscopic developing metastases may be described as follows: micrometastases undergoing surgery-driven active vascularization (sensitive to adjuvant chemotherapy); activated nanometastases, in transit to micrometastases (sensitive to adjuvant chemotherapy); activated nanometastases needing further evolution to transit to micrometastases (sensitive to adjuvant chemotherapy); activated nanometastases needing further extensive evolution to transit to micrometastases (mostly refractory to adjuvant chemotherapy).

Artificial Intelligence for predicting cancer dynamics



Original article

Annals of Oncology 14: 1484–1493, 2003
DOI: 10.1093/annonc/mdg422

Prognosis in node-negative primary breast cancer: a neural network analysis of risk profiles using routinely assessed factors

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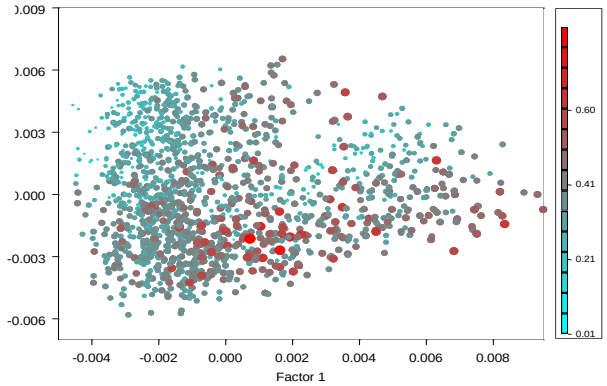
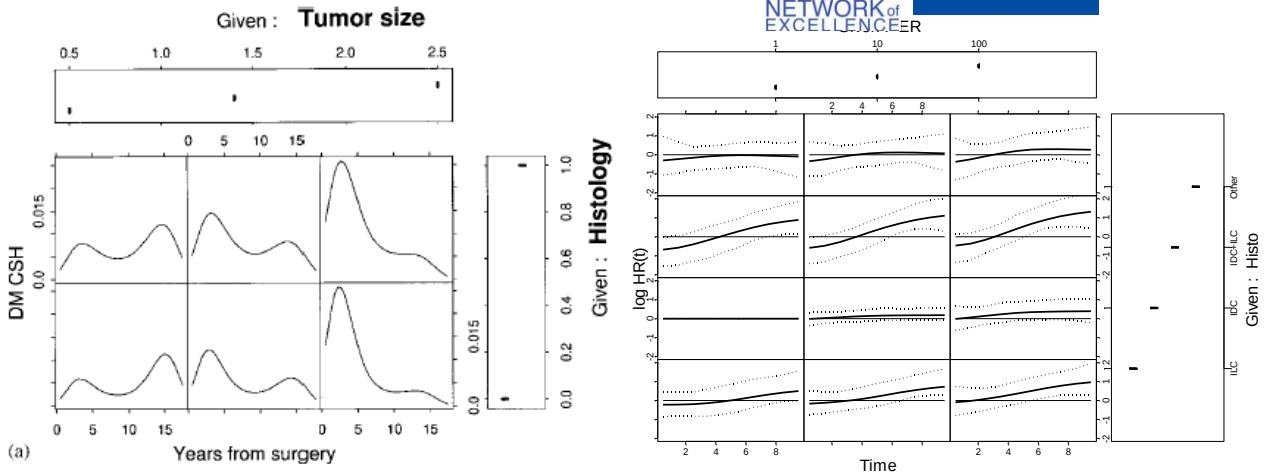
Received 6 February 2003; revised 30 May 2003; accepted 18 July 2003

EU FP6 NoE **BIOPATTERN**
Computational Intelligence for BioPattern Analysis to Support eHealthcare





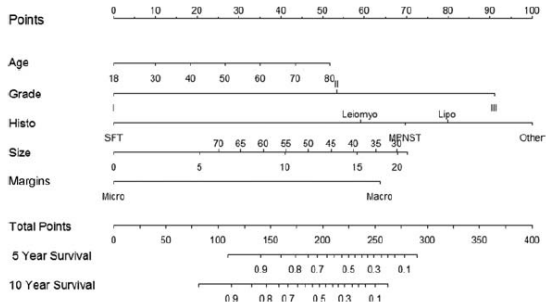


Figure 2. A nomogram for predicting the 5-year and 10-year overall survival for patients with retroperitoneal soft tissue sarcoma is shown. Histo indicates histology; Leiomyo, leiomyosarcoma; Lipo, liposarcoma; SFT, solitary fibrous tumor; MPNST, malignant peripheral nerve sheath tumor; Micro, microscopic; Macro, macroscopic.

CellPress

Cancer Cell

Review

The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth

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*Correspondence: k.d.visser@nki.nl (K.E.d.V.), johanna.joyce@unil.ch (J.A.J.)
https://doi.org/10.1016/j.ccell.2023.02.016

SUMMARY

Cancers represent complex ecosystems comprising tumor cells and a multitude of non-cancerous cells, embedded in an altered extracellular matrix. The tumor microenvironment (TME) includes diverse immune cell types, cancer-associated fibroblasts, endothelial cells, pericytes, and various additional tissue-resident cell types. These host cells were once considered bystanders of tumorigenesis but are now known to play critical roles in the pathogenesis of cancer. The cellular composition and functional state of the TME can differ extensively depending on the organ in which the tumor arises, the intrinsic features of cancer cells, the tumor stage, and patient characteristics. Here, we review the importance of the TME in each stage of cancer progression, from tumor initiation, progression, invasion, and intravasation to metastatic dissemination and outgrowth. Understanding the complex interplay between tumor cell-intrinsic, cell-extrinsic, and systemic mediators of disease progression is critical for the rational development of effective anti-cancer treatments.

CellPress

Cancer Cell

Review

Immune determinants of the pre-metastatic niche

Laura Patras,[1,2,3] Lee Shaashua,[1,3] Irina Matei,[1,*] and David Lyden[1,*]
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[2]Department of Molecular Biology and Biotechnology, Center of Systems Biology, Biodiversity and Bioresources, Faculty of Biology and Geology, Babes-Bolyai University, Cluj-Napoca, Romania
[3]These authors contributed equally
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https://doi.org/10.1016/j.ccell.2023.02.018

SUMMARY

https://doi.org/10.1016/j.ccell.2023.02.018

Primary tumors actively and specifically prime pre-metastatic niches (PMNs), the future sites of organotropic metastasis, preparing these distant microenvironments for disseminated tumor cell arrival. While initial studies of the PMN focused on extracellular matrix alterations and stromal reprogramming, it is increasingly clear that the far-reaching effects of tumors are in great part achieved through systemic and local PMN immunosuppression. Here, we discuss recent advances in our understanding of the tumor immune microenvironment and provide a comprehensive overview of the immune determinants of the PMN's spatiotemporal evolution. Moreover, we depict the PMN immune landscape, based on functional pre-clinical studies as well as mounting clinical evidence, and the dynamic, reciprocal crosstalk with systemic changes imposed by cancer progression. Finally, we outline emerging therapeutic approaches that alter the dynamics of the interactions driving PMN formation and reverse immunosuppression programs in the PMN ensuring early anti-tumor immune responses.

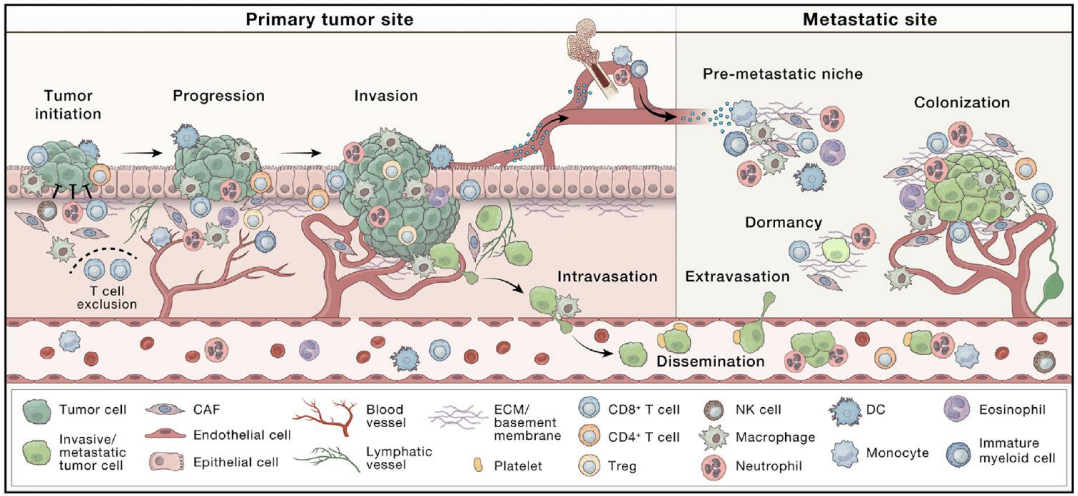

Figure 1. Microenvironmental regulation of primary tumor progression and metastasis

The evolving tumor microenvironment (TME) during all stages of cancer progression is depicted with key representative cell types shown. The TME includes diverse immune cells, cancer-associated fibroblasts (CAFs), endothelial cells, and the extracellular matrix (ECM), among others. These components may vary by tissue type and co-evolve with the tumor as it progresses. The normal tissue microenvironment can constrain cancer outgrowth through the suppressive functions of immune cells, fibroblasts, and the ECM. However, for cancer to advance, it must evade these functions and instead influence cells in the TME to become tumor promoting, resulting in increased proliferation, invasion, and intravasation at the primary site. Cells and factors of the TME also play a vital role in preparing the premetastatic niche, regulating cancer cell survival in the circulation, and promoting extravasation. During the metastatic stages, the TME helps to control metastatic cell dormancy, emergence from this state, and subsequent metastatic outgrowth. Additional molecular details can be found in Figures 2 and 3 and Table 1.

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SCIENTIFIC REPORTS

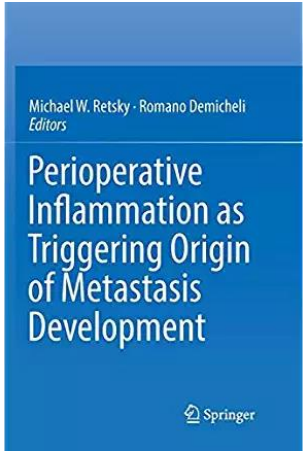
OPEN

NSAIDs Use and Reduced Metastasis in Cancer Patients: results from a meta-analysis

Received: 3 January 2017
Accepted: 3 April 2017
Published online: 12 May 2017

Xiaoping Zhao[1], Zhi Xu[2] & Haoseng Li[1]

This meta-analysis investigated the relationship between non-steroidal anti-inflammatory drugs (NSAIDs) and lymph node/distant metastasis. Relevant sources were identified from MEDLINE, EMBASE, PubMed, and Cochrane Library. Studies that reported the odds ratio (OR)/risk ratio (RR)/ hazard ratio (HR) with 95% confidence intervals (CIs) for the associations of interested outcomes were included. Pooled effect estimates were obtained by using random- or fixed-effect model depending on the heterogeneity across these studies. Sixteen studies involving 202780 participants, including prostate, breast, lung, and colorectal cancer patients, were included. Compared with the reference, generally patients exposed to NSAIDs at pre- and post-diagnosis experienced a significantly reduced risk of distant metastasis (RR 0.708, 95% CI 0.586–0.856 and RR: 0.484, 95% CI: 0.393–0.595, respectively), including prostate cancer (pre-diagnostic use: RR = 0.874, 95% CI, 0.787–0.97; post-diagnostic use: RR = 0.482, 95% CI 0.359–0.647), and breast cancer (pre-diagnostic use: RR = 0.644, 95% CI 0.565–0.735; post-diagnostic use: RR = 0.485, 95% CI 0.362–0.651). However, lymph node metastasis was weakly related with pre-diagnostic use of NSAIDs (RR = 0.949, 95% CI 0.914–0.985). NSAIDs are related to a significantly reduced risk of metastasis development, regardless of pre-diagnostic or post-diagnostic use. However, NSAIDs and lymph node metastasis are weakly associated. Our finding suggested a novel metastasis management.



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

The systemic response to surgery triggers the outgrowth of distant immune-controlled tumors in mouse models of dormancy

Jordan A. Krall,[1] Ferenc Reinhardt,[1] Oblaise A. Mercury,[1] Diwakar R. Pattabiraman,[1] Mary W. Brooks,[1] Michael Dougan,[1,2] Arthur W. Lambert,[1] Brian Bierie,[1] Hidde L. Ploegh,[1,3]* Stephanie K. Dougan,[1,4] Robert A. Weinberg[1,3,5†]

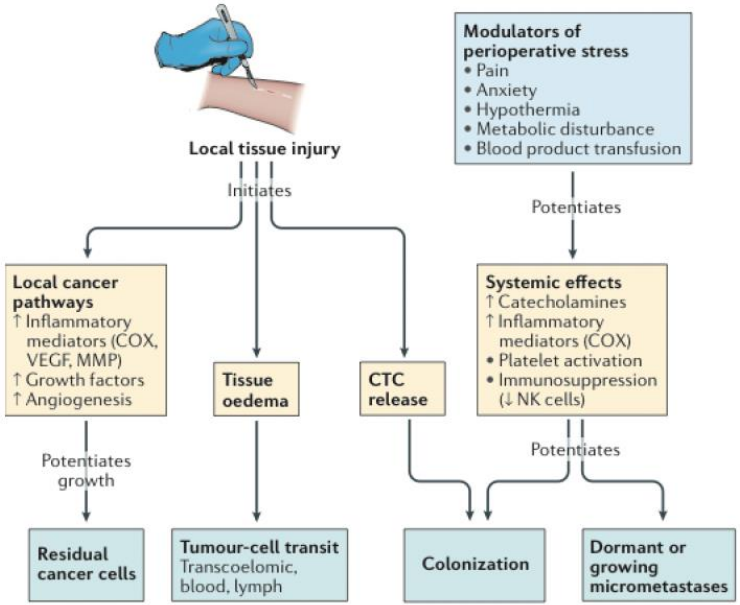
Patients undergoing surgical resection of primary breast tumors confront a risk for metastatic recurrence that peaks sharply 12 to 18 months after surgery. The cause of early metastatic relapse in breast cancer has long been debated, with many ascribing these relapses to the natural progression of the disease. Others have proposed that some aspect of surgical tumor resection triggers the outgrowth of otherwise-dormant metastases, leading to the synchronous pattern of relapse. Clinical data cannot distinguish between these hypotheses, and previous experimental approaches have not provided clear answers. Such uncertainty hinders the development and application of therapeutic approaches that could potentially reduce early metastatic relapse. We describe an experimental model system that definitively links surgery and the subsequent wound-healing response to the outgrowth of tumor cells at distant anatomical sites. Specifically, we find that the systemic inflammatory response induced after surgery promotes the emergence of tumors whose growth was otherwise restricted by a tumor-specific T cell response. Furthermore, we demonstrate that perioperative anti-inflammatory treatment markedly reduces tumor outgrowth in this model, suggesting that similar approaches might substantially reduce early metastatic recurrence in breast cancer patients.

Perioperative events

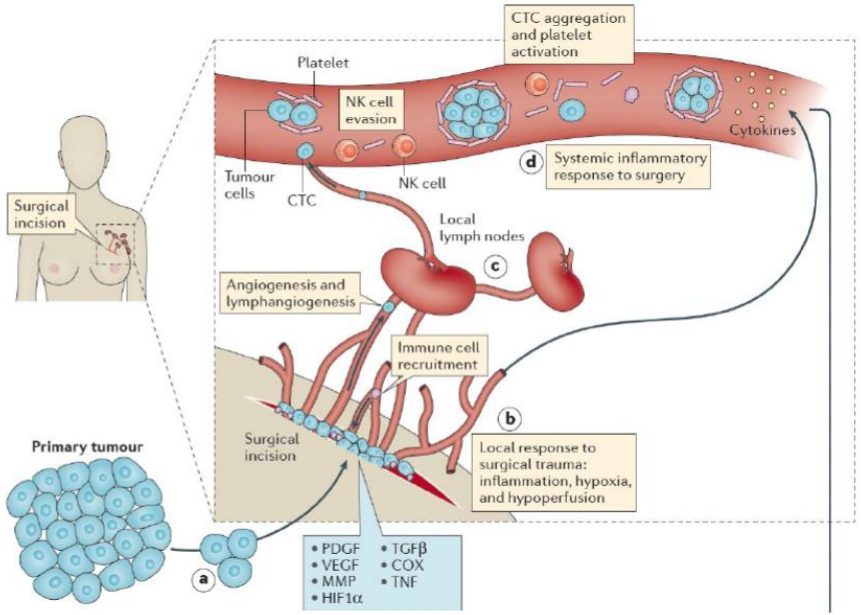
Perioperative events influence cancer recurrence risk after surgery

Jonathan G. Hiller[1,2,3,4], Nicholas J. Perry[5]*, George Poulogiannis[5,6], Bernhard Riedel[1–3] and Erica K. Sloan[1,3,7]*

Abstract | Surgery is a mainstay treatment for patients with solid tumours. However, despite surgical resection with a curative intent and numerous advances in the effectiveness of (neo) adjuvant therapies, metastatic disease remains common and carries a high risk of mortality. The biological perturbations that accompany the surgical stress response and the pharmacological effects of anaesthetic drugs, paradoxically, might also promote disease recurrence or the progression of metastatic disease. When cancer cells persist after surgery, either locally or at undiagnosed distant sites, neuroendocrine, immune, and metabolic pathways activated in response to surgery and/or anaesthesia might promote their survival and proliferation. A consequence of this effect is that minimal residual disease might then escape equilibrium and progress to metastatic disease. Herein, we discuss the most promising proposals for the refinement of perioperative care that might address these challenges. We outline the rationale and early evidence for the adaptation of anaesthetic techniques and the strategic use of anti-adrenergic, anti-inflammatory, and/or antithrombotic therapies. Many of these strategies are currently under evaluation in large-cohort trials and hold promise as affordable, readily available interventions that will improve the postoperative recurrence-free survival of patients with cancer.



Primary surgery can have pro-metastatic features



Importance of the peri-operative period, where chemotherapy nor radiotherapy can be given
(can prevent tissue healing or generate adverse and/or pyrogenic effects which cannot be distinguished from signs of infection)

Hiller *et al*. Nat Rev Clin Oncol 2018

Exploiting the critical perioperative period to improve long-term cancer outcomes

Maya Horowitz, Elad Neeman, Eran Sharon and Shamgar Ben-Eliyahu

Abstract | Evidence suggests that the perioperative period and the excision of the primary tumour can promote the development of metastases—the main cause of cancer-related mortality. This Review first presents the assertion that the perioperative timeframe is pivotal in determining long-term cancer outcomes, disproportionally to its short duration (days to weeks). We then analyse the various aspects of surgery, and their consequent paracrine and neuroendocrine responses, which could facilitate the metastatic process by directly affecting malignant tissues, and/or through indirect pathways, such as immunological perturbations. We address the influences of surgery-related anxiety and stress, nutritional status, anaesthetics and analgesics, hypothermia, blood transfusion, tissue damage, and levels of sex hormones, and point at some as probable deleterious factors. Through understanding these processes and reviewing empirical evidence, we provide suggestions for potential new perioperative approaches and interventions aimed at attenuating deleterious processes and ultimately improving treatment outcomes. Specifically, we highlight excess perioperative release of catecholamines and prostaglandins as key deleterious mediators of surgery, and we recommend blockade of these responses during the perioperative period, as well as other low-risk, low-cost interventions. The measures described in this Review could transform the perioperative timeframe from a prominent facilitator of metastatic progression, to a window of opportunity for arresting and/or eliminating residual disease, potentially improving long-term survival rates in patients with cancer.

Horowitz, M. *et al. Nat. Rev. Clin. Oncol.* **12**, 213–226 (2015); published online 20 January 2015; doi:10.1038/nrclinonc.2014.224

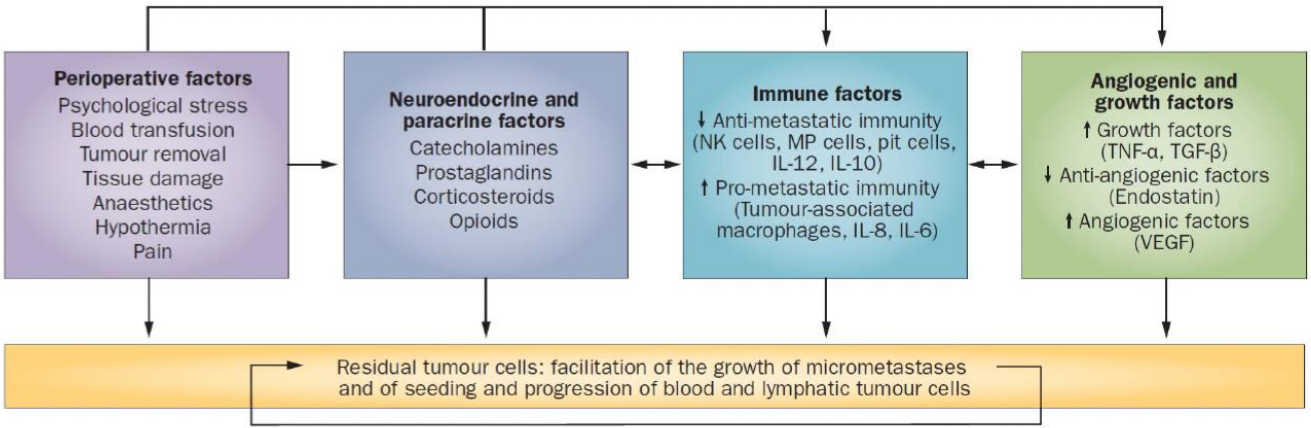


Figure 1 | A schematic presentation of major perioperative risk factors for tumour progression, and some of the neuroendocrine, paracrine, immunological, and angiogenic perturbations they elicit. These perturbations are mutually interactive and eventually affect malignant cells through directly interacting with them and/or through impacting their surrounding milieu.

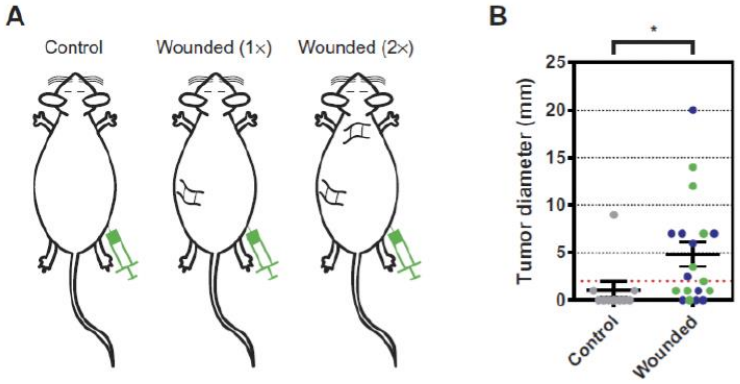
Horowitz *et al.* Nat Rev Clin Oncol 2015

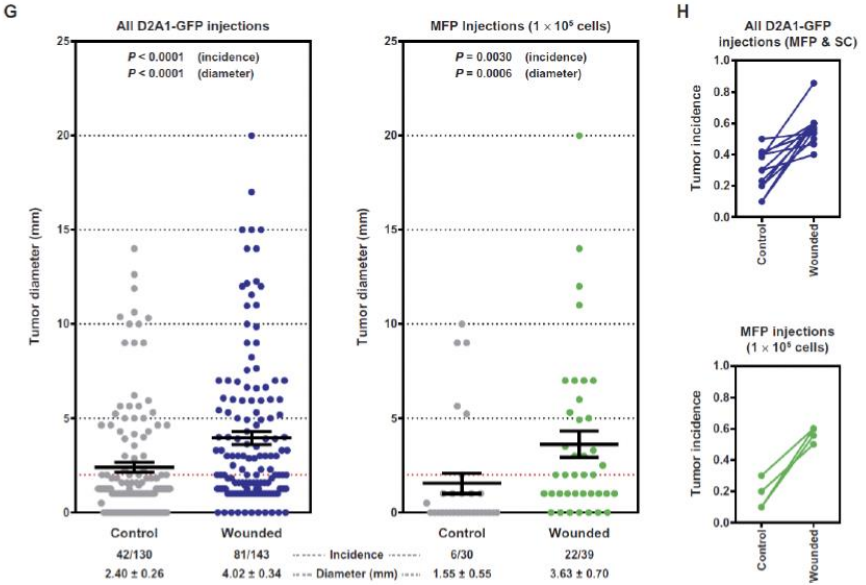
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

The systemic response to surgery triggers the outgrowth of distant immune-controlled tumors in mouse models of dormancy

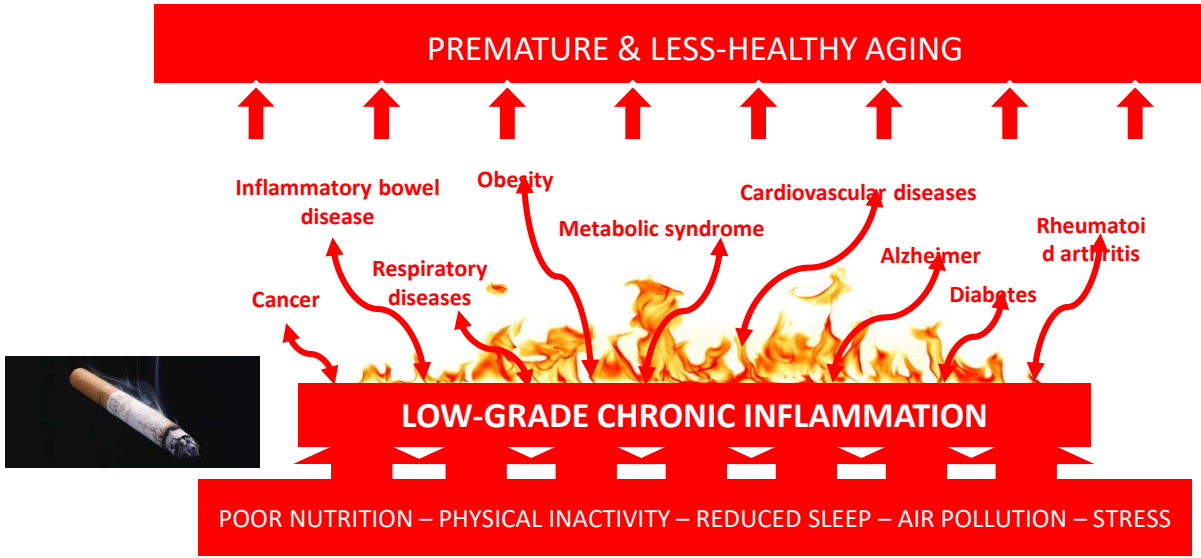
Jordan A. Krall,[1] Ferenc Reinhardt,[1] Oblaise A. Mercury,[1] Diwakar R. Pattabiraman,[1] Mary W. Brooks,[1] Michael Dougan,[1,2] Arthur W. Lambert,[1] Brian Bierie,[1] Hidde L. Ploegh,[1,3]* Stephanie K. Dougan,[1,4] Robert A. Weinberg[1,3,5†]

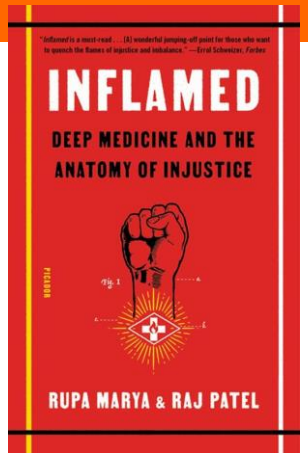




- Systemic inflammatory response induced after surgery (without tumor resection!) promotes the emergence of tumors whose growth was otherwise restricted by a tumor-specific T cell response.
- Perioperative anti-inflammatory treatment reduces tumor outgrowth in this model, suggesting that similar approaches might also reduce early recurrence in BC patients.

PROBLEM: Low-grade chronic inflammation

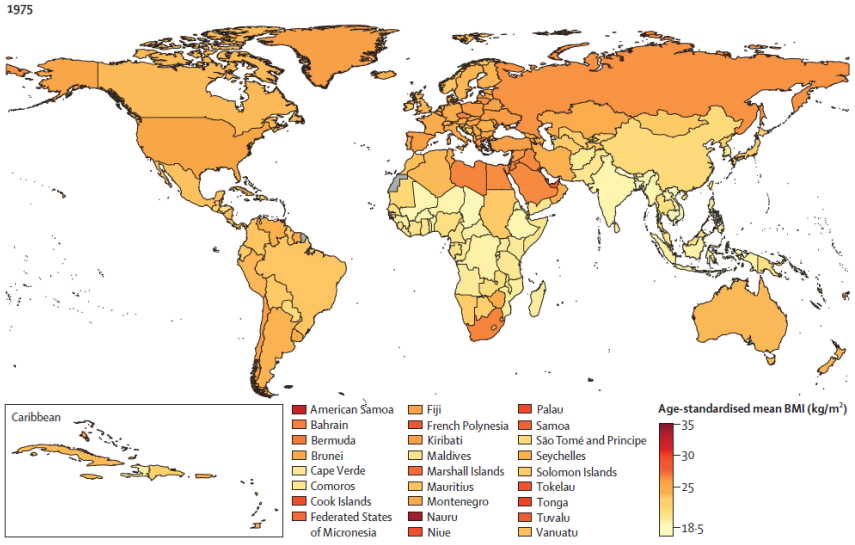




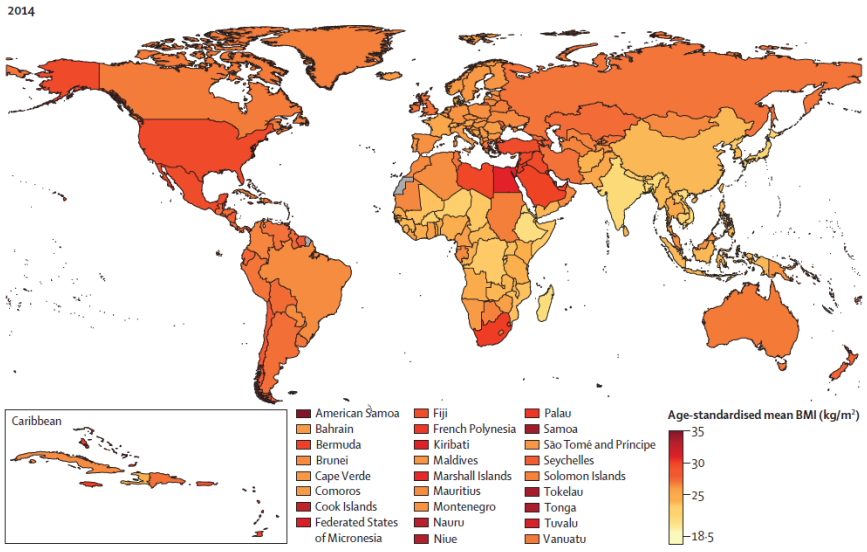
NCD Risk Factor Collaboration Lancet 2016

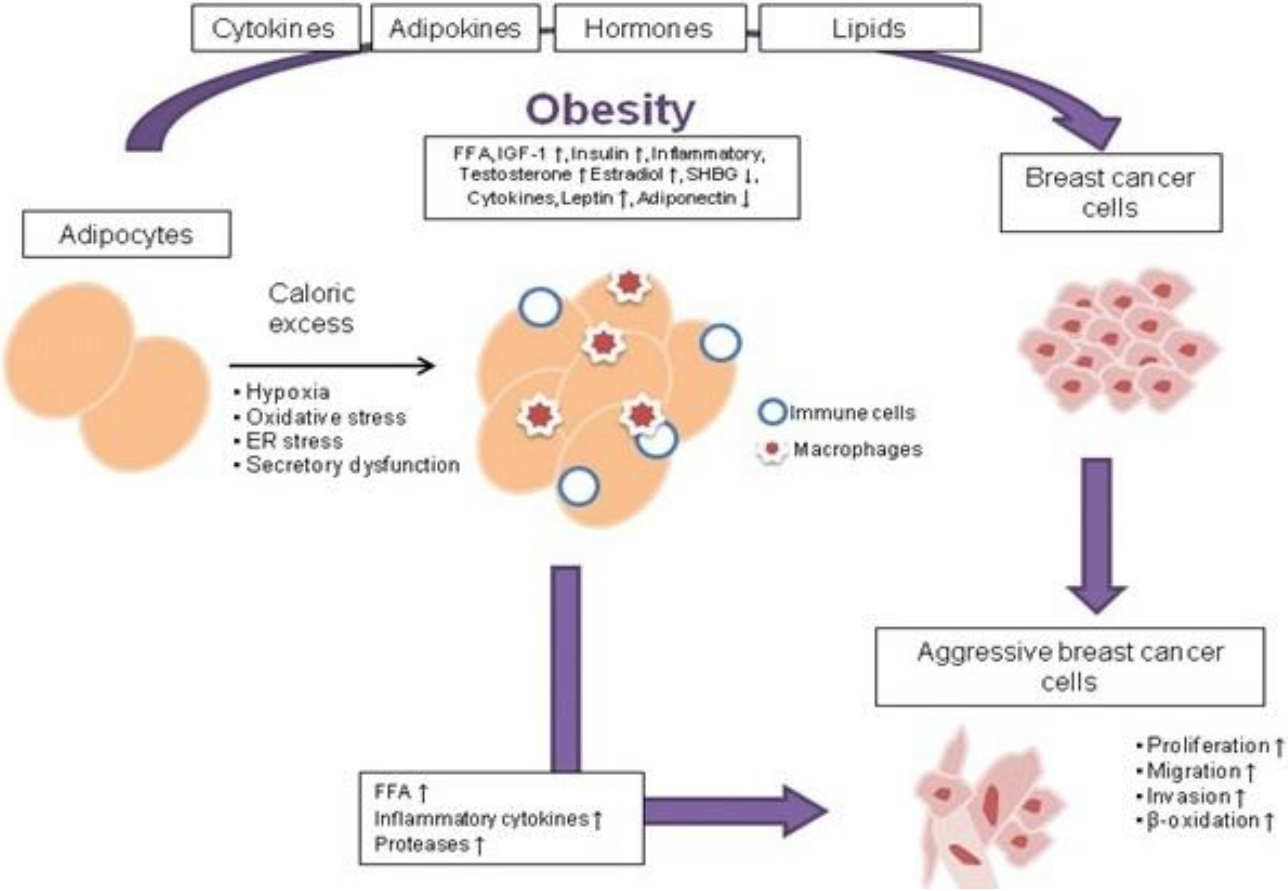
Age-standardized mean BMI in women

1975



2014




Cytokines
Adipokines
Hormones
Lipids
Obesity
FFA,IGF-1 ↑,Insulin ↑,Inflammatory,
Testosterone ↑Estradiol ↑,SHBG ↓,
Cytokines,Leptin ↑,Adiponectin ↓
Breast cancer cells
Adipocytes
Caloric excess
• Hypoxia
• Oxidative stress
• ER stress
• Secretory dysfunction
Immune cells
Macrophages
Aggressive breast cancer cells
FFA ↑
Inflammatory cytokines ↑
Proteases ↑
• Proliferation ↑
• Migration ↑
• Invasion ↑
• β-oxidation ↑

European Journal of Cancer 87 (2017) 10–20

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journal homepage: www.ejcancer.com

Original Research

Recurrence dynamics of breast cancer according to baseline body mass index☆

Elia Biganzoli [a,**,1], Christine Desmedt [b,*,1], Marco Fornili [a], Evandro de Azambuja [c], Nathalie Cornez [d], Fernand Ries [e], Marie-Thérèse Closon-Dejardin [f], Joseph Kerger [c], Christian Focan [g], Angelo Di Leo [h], Jean-Marie Nogaret [i], Christos Sotiriou [b], Martine Piccart [c], Romano Demicheli [a]

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[h] Sandro Pitigliani Medical Oncology Unit, Hospital of Prato, Instituto Toscano Tumori, 59100 Prato, Italy
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Available online 31 October 2017

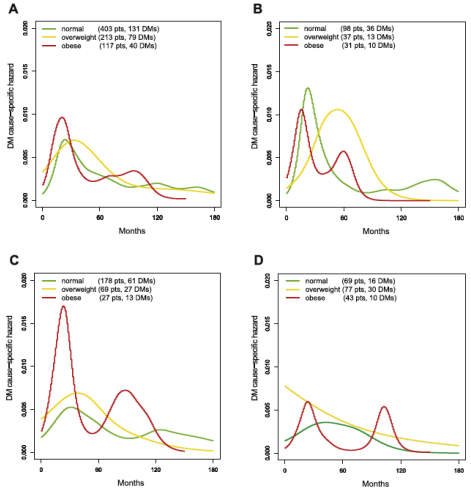

Fig. 4. Cause-specific hazard estimates for distant metastases over time in all patients (A), in the subgroups of oestrogen receptor (ER)-negative breast cancer (B) and pre- and postmenopausal ER-positive breast cancer (C and D, respectively). Estimates were obtained by the piecewise exponential model with P-splines.

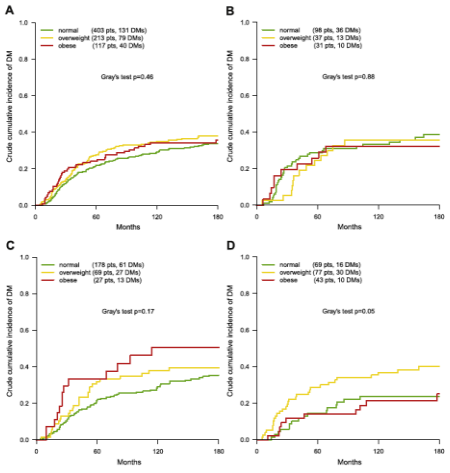

Fig. 3. Estimated crude cumulative incidence of distant metastases in all patients (A), in the subgroups of oestrogen receptor (ER)-negative breast cancer (B) and pre- and postmenopausal ER-positive breast cancer (C and D, respectively). The number of events specified for each BMI category is that occurring in the first 15 years of follow-up. DM, distant metastasis.

Differential Benefit of Adjuvant Docetaxel-Based Chemotherapy in Patients With Early Breast Cancer According to Baseline Body Mass Index

Christine Desmedt, PhD[1]; Marco Fornili, PhD[2]; Florian Clatot, MD, PhD[1,3]; Romano Demicheli, MD[2]; Davide De Bortoli, PhD[2]; Angelo Di Leo, MD, PhD[4]; Giuseppe Viale, MD[5]; Evandro de Azambuja, MD, PhD[6]; John Crown, MBBCh, MD[7]; Prudence A. Francis, MD[8]; Christos Sotiriou, MD, PhD[9]; Martine Piccart, MD, PhD[10]; and Elia Biganzoli, PhD[2]

J Clin Oncol 38:2883-2891. © 2020 by American Society of Clinical Oncology

OXFORD

JNCI J Natl Cancer Inst (2018) 110(10): djy042

doi: 10.1093/jnci/djy042
Article

ARTICLE

Potential Benefit of Intra-operative Administration of Ketorolac on Breast Cancer Recurrence According to the Patient's Body Mass Index

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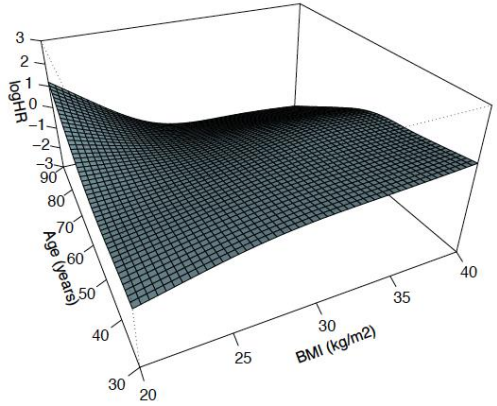

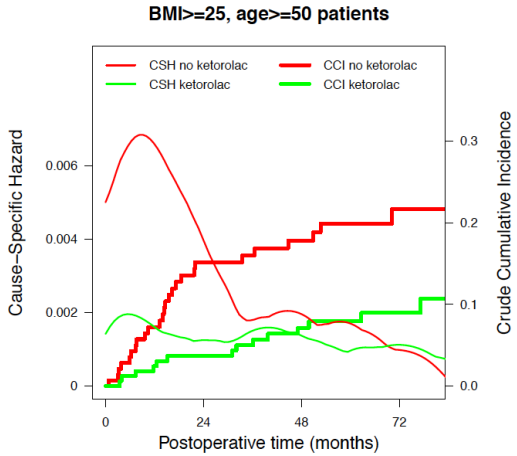

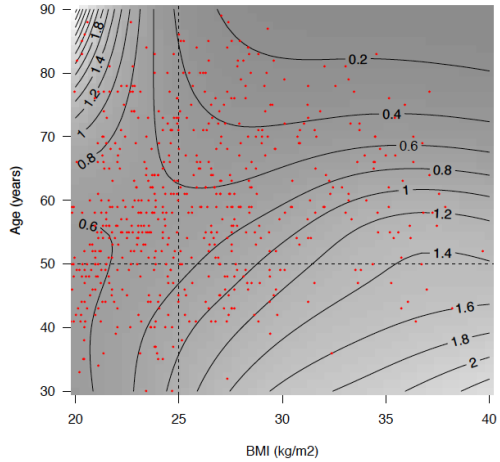

nature medicine

REVIEW ARTICLE
https://doi.org/10.1038/s41591-018-0014-x

Understanding the tumor immune microenvironment (TIME) for effective therapy

Mikhail Binnewies[1], Edward W. Roberts[1], Kelly Kersten[1], Vincent Chan[2], Douglas F. Fearon[3], Miriam Merad[4], Lisa M. Coussens[5], Dmitry I. Gabrilovich[6], Suzanne Ostrand-Rosenberg[7,8], Catherine C. Hedrick[9], Robert H. Vonderheide[10], Mikael J. Pittet[11], Rakesh K. Jain[12], Weiping Zou[13], T. Kevin Howcroft[14], Elisa C. Woodhouse[14], Robert A. Weinberg[15]* and Matthew F. Krummel[1,2]*

The clinical successes in immunotherapy have been both astounding and at the same time unsatisfactory. Countless patients with varied tumor types have seen pronounced clinical response with immunotherapeutic intervention; however, many more patients have experienced minimal or no clinical benefit when provided the same treatment. As technology has advanced, so has the understanding of the complexity and diversity of the immune context of the tumor microenvironment and its influence on response to therapy. It has been possible to identify different subclasses of immune environment that have an influence on tumor initiation and response and therapy; by parsing the unique classes and subclasses of tumor immune microenvironment (TIME) that exist within a patient's tumor, the ability to predict and guide immunotherapeutic responsiveness will improve, and new therapeutic targets will be revealed.

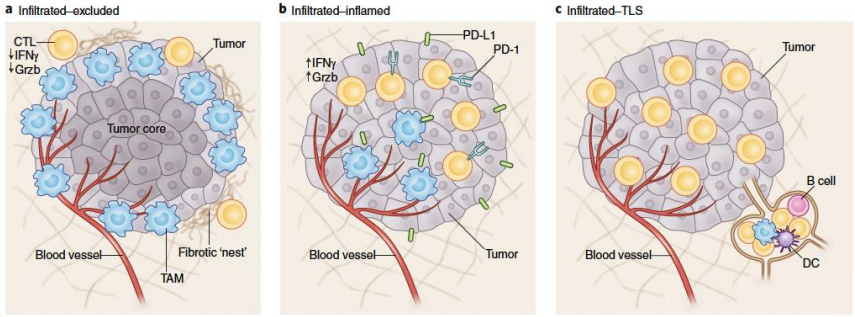

Fig. 1 | General classes of TIME. Three classes of TIME are displayed. **a**, I–E TIMEs are characterized by the exclusion of CTLs from the tumor core. CTLs in I–E TIMEs are instead present along the tumor periphery, where they can be found in contact with Ly6C^{lo} F4/80^{+} tumor-associated macrophages or 'stuck' in fibrotic nests. **b**, In comparison, I–I TIMEs are defined by an abundance of PD-L1 expression on tumor and myeloid cells and highly activated CTLs characterized by expression of Grzb, IFNγ and PD-1. In some subsets of I–I TIME, tumor cells will have defects in DNA mismatch repair (MSI-H), thus resulting in an increased number of neoepitopes. **c**, TLS-TIMEs have histological evidence of containing TLSs, aggregates of immune cells with a composition similar to that in lymph nodes, including B cells, dendritic cells and T_{reg} cells.

Signal Transduction and Targeted Therapy

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REVIEW ARTICLE **OPEN**

Advantages of targeting the tumor immune microenvironment over blocking immune checkpoint in cancer immunotherapy

Tianyu Tang[1,2,3,4], Xing Huang[1,2,3,4], Gang Zhang[1,2,3,4], Zhengtao Hong[1,2,3,4], Xueli Bai[1,2,3,4] and Tingbo Liang[1,2,3,4]

Despite great success in cancer immunotherapy, immune checkpoint-targeting drugs are not the most popular weapon in the armory of cancer therapy. Accumulating evidence suggests that the tumor immune microenvironment plays a critical role in anti-cancer immunity, which may result in immune checkpoint blockade therapy being ineffective, in addition to other novel immunotherapies in cancer patients. In the present review, we discuss the deficiencies of current cancer immunotherapies. More importantly, we highlight the critical role of tumor immune microenvironment regulators in tumor immune surveillance, immunological evasion, and the potential for their further translation into clinical practice. Based on their general targetability in clinical therapy, we believe that tumor immune microenvironment regulators are promising cancer immunotherapeutic targets. Targeting the tumor immune microenvironment, alone or in combination with immune checkpoint-targeting drugs, might benefit cancer patients in the future.

Signal Transduction and Targeted Therapy (2021)6:72 ; https://doi.org/10.1038/s41392-020-00449-4

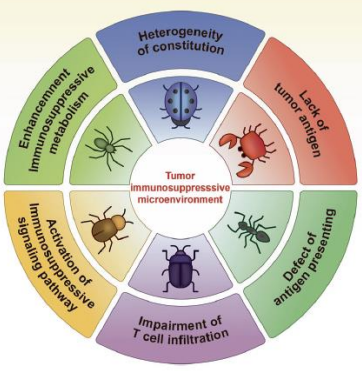
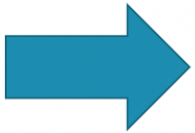


Fig. 1 Hallmarks of an immunosuppressive tumor microenvironment. Six hallmarks, including heterogeneity of constitution, lack of tumor antigen, defect of antigen-presenting cell, impairment of T-cell infiltration, activation of an immunosuppressive signaling pathway, and enhancement of immunosuppressive metabolism co-contribute to an immunosuppressive tumor microenvironment

Immune microenvironment & obesity

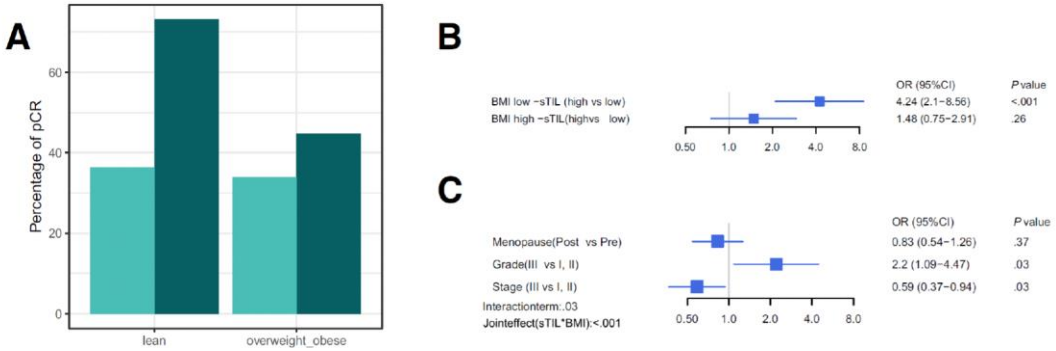
- **445 TNBC patients** treated with neo-adjuvant chemotherapy
- **sTIL** scored centrally on pre-treatment biopsies
- sTIL: low (<30%) versus high (≥30%)
- **BMI**: lean (18.5-25 kg/m^2) versus overweight and obese (≥25 kg/m^2)) and continuous variables.
- **pCR** (ypT0/isN0): 41%



Does BMI have an impact on the value of sTIL to predict pCR in TNBC patients treated with NACT?

Floris et al. JNCI 2020

sTIL is not predictive of pCR in pts with high BMI



Summary BMI, sTIL & pCR to neoadj. chemo

- sTIL are known to be predictive for pCR in patients with TNBC treated with neoadjuvant chemotherapy.
- High sTIL were statistically significantly associated with pCR in lean but not in heavier patients in the multivariable analysis.
- High sTIL were further associated with increased event-free survival in lean but not in heavier patients.
- Adiposity is most probably associated with a distinct immune microenvironment since BMI is modifying the effect of sTIL.

OXFORD

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Article

Body Mass Index and Tumor-Infiltrating Lymphocytes in Triple-Negative Breast Cancer

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Abstract

Background: High levels of stromal tumor-infiltrating lymphocytes (sTIL) are associated with increased pathological complete response (pCR) rate and longer survival after neoadjuvant chemotherapy in triple-negative breast cancer (TNBC) patients. Here, we evaluated the value of sTIL in predicting pCR and explored prognosis in TNBC patients treated with neoadjuvant chemotherapy according to body mass index (BMI). **Methods:** sTIL were scored centrally on pretreatment biopsies from 2 retrospective series of nonunderweight TNBC patients (n = 445). sTIL and BMI were considered as binary (sTIL: <30.0% vs ≥30.0%; BMI: lean vs overweight and obese) and continuous variables. Associations with pCR (ypT0/isN0) were assessed using logistic regression, and associations with event-free survival and overall survival were assessed using Cox regressions. **Results:** 236 (53.0%) patients were lean and 209 (47.0%) overweight and obese. pCR was achieved in 181 of 445 (41.7%) patients. Median sTIL was 11.0%, and 99 of 445 (22.2%) tumors had high sTIL. A statistically significant interaction between sTIL and BMI, considered as categorical or continuous variables, for predicting pCR was observed in the multivariable analysis ($P_{interaction}$ = .03 and .04, respectively). High sTIL were statistically significantly associated with pCR in lean (odds ratio [OR] = 4.24, 95% confidence interval [CI] = 2.10 to 8.56; P < .001) but not in heavier patients (OR = 1.48, 95% CI = 0.75 to 2.91; P = .26) in the multivariable analysis. High sTIL were further associated with increased event-free survival in lean (hazard ratio [HR] = 0.22, 95% CI = 0.08 to 0.62; P = .004) but not in heavier patients (HR = 0.53, 95% CI = 0.26 to 1.08; P = .08). Similar results were obtained for overall survival. **Conclusion:** BMI is modifying the effect of sTIL on pCR and prognosis in TNBC patients treated with neoadjuvant chemotherapy.

Stromal tumor-infiltrating lymphocytes (sTIL) have been extensively studied during the last decade in early breast cancer (1). These are generally quantified using a standardized method on hematoxylin and eosin-stained whole tissue sections (2). sTIL are more prevalent in triple-negative (TNBC) and human epidermal growth factor receptor 2 (HER2)-positive breast cancers as compared to estrogen receptor (ER)-positive breast tumors (3, 4). A pooled analysis of sTIL in TNBC patients treated with adjuvant chemotherapy in the context of clinical trials confirmed the prognostic role of sTIL in these patients and the

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ARTICLE

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Review

Cancer Research

Can Exercise-Induced Modulation of the Tumor Physiologic Microenvironment Improve Antitumor Immunity?

Xiaojie Zhang[1], Kathleen A. Ashcraft[1], Allison Betof Warner[2], Smita K. Nair[1], and Mark W. Dewhirst[1]

Abstract

The immune system plays an important role in controlling cancer growth. However, cancers evolve to evade immune detection. Immune tolerance and active immune suppression results in unchecked cancer growth and progression. A major contributor to immune tolerance is the tumor physiologic microenvironment, which includes hypoxia, hypoglucosis, lactosis, and reduced pH. Preclinical and human studies suggest that exercise elicits mobilization of leukocytes into circulation (also known as "exercise-induced leukocytosis"), especially cytotoxic T cells and natural killer cells. However, the tumor physiologic microenvironment presents a significant barrier for these cells to enter the tumor and, once there, properly function. We hypothesize that the effect of exercise on the immune system's ability to control cancer growth is linked to how exercise affects the tumor physiologic microenvironment. Normalization of the microenvironment by exercise may promote more efficient innate and adaptive immunity within the tumor. This review summarizes the current literature supporting this hypothesis.

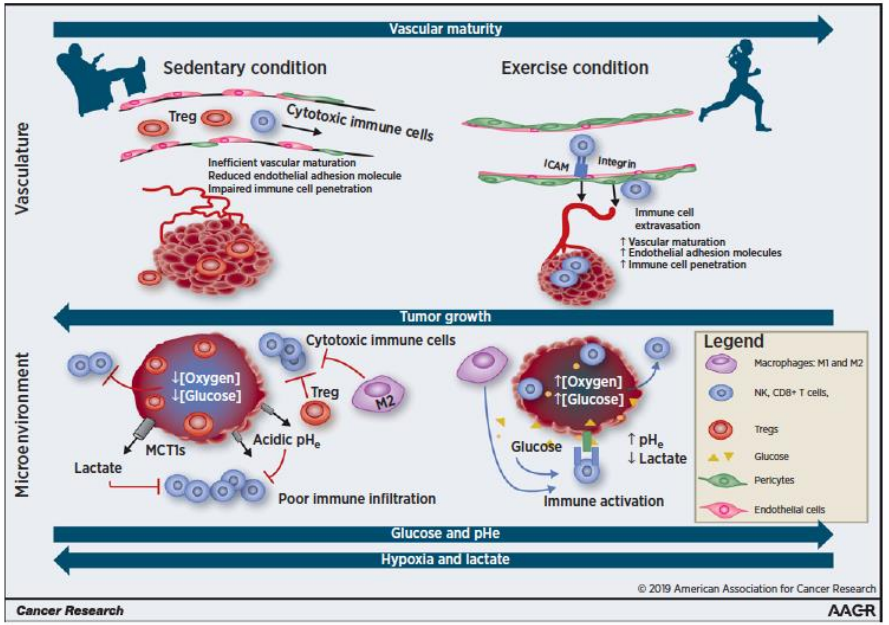

Figure 1.

Exercise primes the tumor toward a more aerobic, less glycolytic physiologic microenvironment. The schematic demonstrates the large-scale vascular (top) and microscale physiologic microenvironment (bottom) changes within the tumor of an exercised versus sedentary individual. It is not drawn to scale. Exercise, in normalizing tumor vasculature, increases endothelial adhesion molecule expression, promotes the extravasation of cytotoxic immune cell (NK cells, $CD8^+$ T cells, and type1 macrophages) and infiltration of these cells into the tumor. Conversely, under the sedentary condition, tumors manifest a hypoxic, aberrantly vascularized, and highly glycolytic tumor. The two tumor cross-sections on the bottom represent the physiologic microenvironment of a sedentary versus exercised individual. High lactate, low pHe, and hypoglucotic environment within the sedentary tumor promote immune-suppressive Tregs but inhibit the function of tumor-infiltrating cytotoxic immune cells. The immune cells that are in the sedentary tumor microenvironment are metabolically outcompeted by the highly proliferative cancer cells. Exercise, by normalizing tumor vasculature, yields a better perfused tumor, with improved energy substrate (glucose availability), improved oxygen concentrations, and decreased glycolytic lactate production. The net effect of this is an enhanced metabolic and immunologic environment, one that results in more potent immune activation and more effective tumor cell cytolysis.

Journal of
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Does Physical Activity Have an Impact on Recurrence Dynamics in Early Breast Cancer Patients?

Elia Biganzoli; Christine Desmedt; Romano Demicheli

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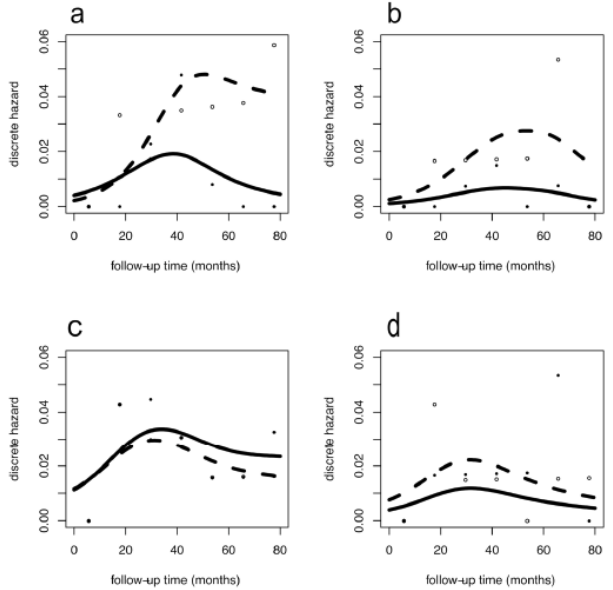
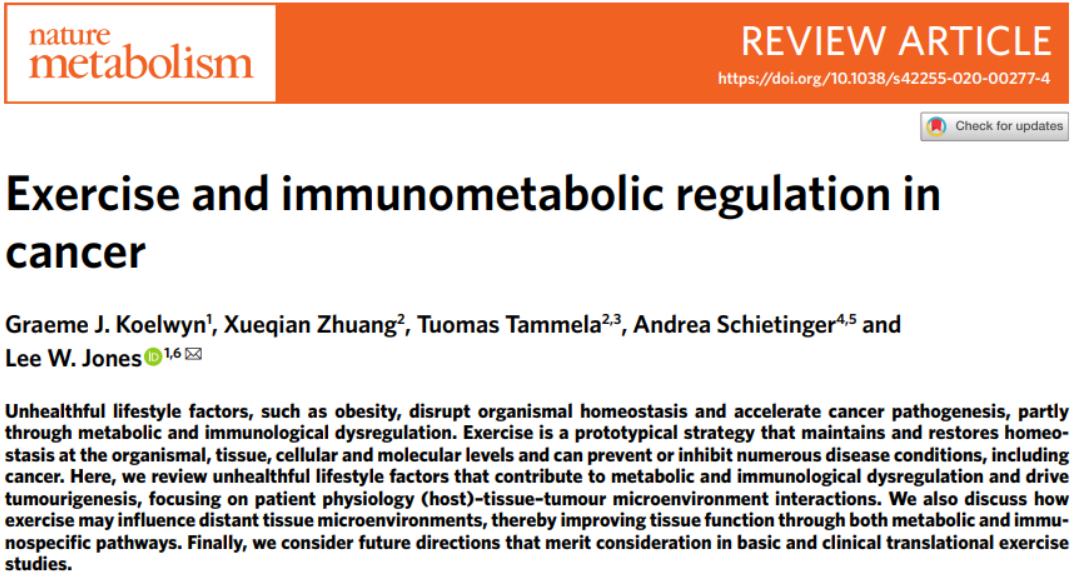


Figure 1. Recurrence and overall mortality dynamics in the urban and rural Australian trials. Hazard rate patterns for disease-free survival (DFS) (left panels: (**a**,**c**)) and odds ratios (OS) (right panels: (**b**,**d**)) for 194 urban women (upper panels: (**a**,**b**)) and 143 rural women (bottom panels: (**c**,**d**)). Discrete cause-specific hazard rates were estimated within a yearly interval, empirical estimates are represented as small open circles for no exercise and filled circles for exercise. Smoothed curves were obtained by flexible regression procedure based on generalized additive models, dashed lines for no exercise and continuous lines for exercise. *X* axis: time in months; *y* axis: discrete hazard rates (estimated annual conditional event probabilities).

What is exercise?

- Exercise is a structured, repeated and purposeful physical activity with the objective of improving health.
- It is often a combination of supervised aerobic and resistance exercise.



nature metabolism

REVIEW ARTICLE

https://doi.org/10.1038/s42255-020-00277-4

Check for updates

Exercise and immunometabolic regulation in cancer

Graeme J. Koelwyn[1], Xueqian Zhuang[2], Tuomas Tammela[2,3], Andrea Schietinger[4,5] and Lee W. Jones[1,6]

Unhealthful lifestyle factors, such as obesity, disrupt organismal homeostasis and accelerate cancer pathogenesis, partly through metabolic and immunological dysregulation. Exercise is a prototypical strategy that maintains and restores homeostasis at the organismal, tissue, cellular and molecular levels and can prevent or inhibit numerous disease conditions, including cancer. Here, we review unhealthful lifestyle factors that contribute to metabolic and immunological dysregulation and drive tumourigenesis, focusing on patient physiology (host)–tissue–tumour microenvironment interactions. We also discuss how exercise may influence distant tissue microenvironments, thereby improving tissue function through both metabolic and immunospecific pathways. Finally, we consider future directions that merit consideration in basic and clinical translational exercise studies.

nature medicine
FOCUS | ARTICLES
https://doi.org/10.1038/s41591-019-0633-x

Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells

Vanessa Frodermann[1,14], David Rohde[1,14], Gabriel Courties[1], Nicolas Severe[2,3], Maximilian J. Schloss[1], Hajera Amatullah[4], Cameron S. McAlpine[1], Sebastian Cremer[1], Friedrich F. Hoyer[1], Fei Ji[5,6], Ian D. van Koeverden[7], Fanny Herisson[1], Lisa Honold[1], Gustavo Santos Masson[1], Shuang Zhang[1], Jana Grune[1], Yoshiko Iwamoto[1], Stephen P. Schmidt[1], Gregory R. Wojtkiewicz[1], I-Hsiu Lee[1], Karin Gustafsson[2,3], Gerard Pasterkamp[8], Saskia C. A. de Jager[7,9], Ruslan I. Sadreyev[6,10], Jean MacFadyen[11], Peter Libby[11], Paul Ridker[11], David T. Scadden[2,3], Kamila Naxerova[1], Kate L. Jeffrey[4], Filip K. Swirski[1] and Matthias Nahrendorf[1,12,13]*

A sedentary lifestyle, chronic inflammation and leukocytosis increase atherosclerosis; however, it remains unclear whether regular physical activity influences leukocyte production. Here we show that voluntary running decreases hematopoietic activity in mice. Exercise protects mice and humans with atherosclerosis from chronic leukocytosis but does not compromise emergency hematopoiesis in mice. Mechanistically, exercise diminishes leptin production in adipose tissue, augmenting quiescence-promoting hematopoietic niche factors in leptin-receptor-positive stromal bone marrow cells. Induced deletion of the leptin receptor in *Prrx1*-creER^{T2}; *Lepr*$^{fl/fl}$ mice reveals that leptin's effect on bone marrow niche cells regulates hematopoietic stem and progenitor cell (HSPC) proliferation and leukocyte production, as well as cardiovascular inflammation and outcomes. Whereas running wheel withdrawal quickly reverses leptin levels, the impact of exercise on leukocyte production and on the HSPC epigenome and transcriptome persists for several weeks. Together, these data show that physical activity alters HSPCs via modulation of their niche, reducing hematopoietic output of inflammatory leukocytes.

nature metabolism
REVIEW ARTICLE
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Exercise and cardiac health: physiological and molecular insights

Jose B. N. Moreira[1], Martin Wohlwend[1] and Ulrik Wisløff[1,2] ✉

The cardiac benefits of exercise have been recognized for centuries. Studies have undisputedly shown that regular exercise is

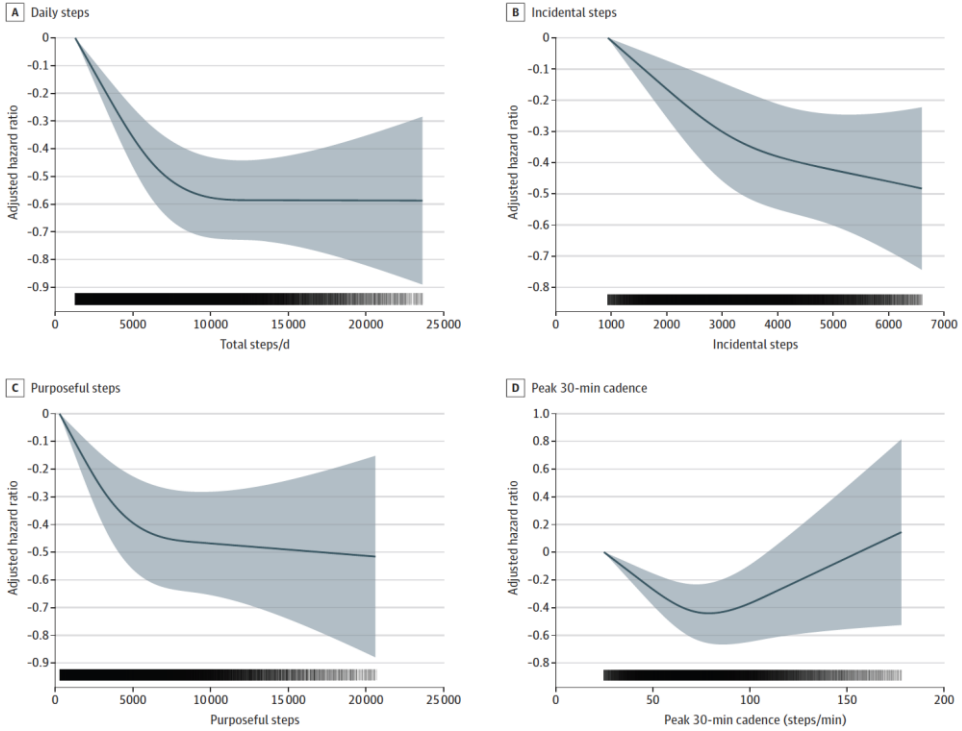
JAMA Internal Medicine | Original Investigation

Prospective Associations of Daily Step Counts and Intensity With Cancer and Cardiovascular Disease Incidence and Mortality and All-Cause Mortality

Borja del Pozo Cruz, PhD; Matthew N. Ahmadi, PhD; I-Min Lee, MBBS, ScD; Emmanuel Stamatakis, PhD

JAMA Intern Med. doi:10.1001/jamainternmed.2022.4000
Published online September 12, 2022.

Figure 1. Dose-Response Associations Between Primary Exposures and All-Cause Mortality



Hazard ratios and associated 95% CIs adjusted for age, sex, race, education, Townsend Deprivation Index, smoking, alcohol use, fruit and vegetable consumption, family history of cancer and CVD, medication use (cholesterol, insulin, hypertension), accelerometer-measured sleep, and wear accelerometer days. For incidental steps, models were further adjusted for purposeful steps (and vice versa). Dose-response associations were assessed with restricted cubic splines with knots at 10th, 50th, and 90th percentiles of the distribution of the exposure of interest. Darker colors in the lower bars represent a higher sample clustering. Shaded areas represent 95% CIs. CVD indicates cardiovascular disease; total steps/d, median number of steps per day across valid days; incidental steps, total daily steps at 1-39 steps/min; purposeful steps, total daily steps at ≥40 steps/min; peak 30-min cadence, average steps/min recorded for the 30 highest, but not necessarily consecutive, min/day.

The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease

Michael Gleeson, Nicolette C. Bishop, David J. Stensel, Martin R. Lindley, Sarabjit S. Mastana and Myra A. Nimmo

Abstract | Regular exercise reduces the risk of chronic metabolic and cardiorespiratory diseases, in part because exercise exerts anti-inflammatory effects. However, these effects are also likely to be responsible for the suppressed immunity that makes elite athletes more susceptible to infections. The anti-inflammatory effects of regular exercise may be mediated via both a reduction in visceral fat mass (with a subsequent decreased release of adipokines) and the induction of an anti-inflammatory environment with each bout of exercise. In this Review, we focus on the known mechanisms by which exercise — both acute and chronic — exerts its anti-inflammatory effects, and we discuss the implications of these effects for the prevention and treatment of disease.

Table 1 | **A summary of the associations between physical activity and major diseases***

Disease	Evidence that physical activity may lower disease risk and/or have therapeutic value in treating disease
CHD	A large body of epidemiological evidence demonstrates that high levels of physical activity and physical fitness are associated with a lower risk of developing CHD. RCTs show that regular physical activity can favourably modify CHD risk factors, including (but not limited to) dyslipidaemia, hypertension and obesity. RCTs also show that physical activity improves survival in CHD patients.
Stroke	Evidence suggests that high levels of physical activity and physical fitness reduce the risk of stroke, although the data are not as compelling as those for CHD. RCTs show that physical activity can lower (but not necessarily normalize) blood pressure in hypertensive individuals.
Cancer	High levels of physical activity are associated with a lower risk of colon and breast cancer. Physical activity may lower cancer risk by systemic mechanisms (such as reduced body fat and insulin levels, and enhanced immune function) and site-specific mechanisms (namely, reduced levels of sex steroid hormones for breast cancer, and decreased bowel transit time for colon cancer). Some observational and RCT evidence supports a therapeutic role for physical activity in preserving mobility and function in cancer patients.
T2D	Observational epidemiological evidence consistently demonstrates an association between high levels of physical activity and/or fitness and a reduced risk of developing T2D. RCTs show that lifestyle intervention (diet and physical activity) can lower body mass, improve glucose tolerance and reduce the risk of developing T2D in high-risk patients. In patients with T2D, high levels of physical activity and physical fitness are associated with a reduced risk of CHD and all-cause mortality.
Dementia	Observational epidemiological studies indicate that higher levels of physical activity are associated with a lower risk of cognitive decline and dementia in older adults. Some limited evidence is available from RCTs to suggest that physical activity induces modest improvements in cognition in individuals who are at increased risk of Alzheimer's disease or other forms of dementia.
Other	There is some evidence from observational and intervention studies to support a role for physical activity in enhancing physical function and improving quality of life in those suffering from chronic heart failure, chronic obstructive pulmonary disease, depression, intermittent claudication, osteoarthritis and osteoporosis.

CHD, coronary heart disease; RCT, randomized controlled trial; T2D, type 2 diabetes mellitus. *See REFS 8,9 for further detail.

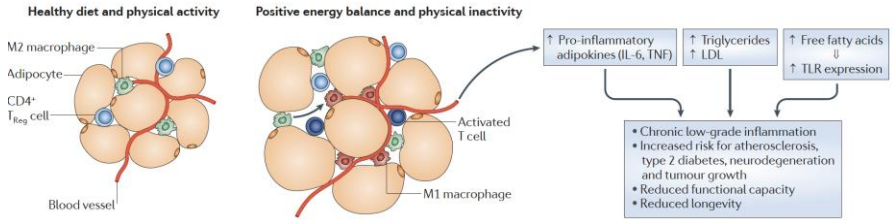


Figure 1 | **The effect of diet and physical activity on inflammation and disease.** A healthy diet and physical activity maintain the anti-inflammatory phenotype of adipose tissue, which is marked by small adipocyte size and the presence of anti-inflammatory immune cells, such as M2-type macrophages and CD4+ regulatory T (T_{Reg}) cells. A positive energy balance and physical inactivity lead to an accumulation of visceral fat and adipose tissue infiltration by pro-inflammatory macrophages and T cells. The pro-inflammatory M1 macrophage phenotype predominates and inflamed adipose tissue releases pro-inflammatory adipokines, such as tumour necrosis factor (TNF), which causes a state of persistent low-grade systemic inflammation. This may promote the development of insulin resistance, tumour growth, neurodegeneration and atherosclerosis. Atherosclerosis is exacerbated by the deleterious changes in the blood lipid profile that are associated with a lack of physical activity. LDL, low-density lipoprotein; IL-6, interleukin-6;TLR, Toll-like receptor.

Can physical activity ameliorate immunosenescence and thereby reduce age-related multi-morbidity?

*Niharika A. Duggal[1], Grace Niemiro[2], Stephen D. R. Harridge[3], Richard J. Simpson[2,4,5] and Janet M. Lord[1,6]**

Abstract | Remodelling of the immune system with age — immunosenescence — is a substantial contributor to poor health in older adults, with increasing risk of infections, cancer and chronic inflammatory disease contributing to age-related multi-morbidity. What is seldom considered when examining the immune response of an aged individual is that the immune system is profoundly influenced by physical activity. Habitual physical activity levels decline with age, with significant consequences for muscle mass and function. Skeletal muscle is a major immune regulatory organ and generates a range of proteins, termed myokines, which have anti-inflammatory and immunoprotective effects. Several studies indicate that maintaining physical activity has immune benefits in older adults, for example, it reduces the systemic inflammation associated with chronic age-related diseases. Here, we discuss how physical activity can prevent or ameliorate age-related multi-morbidity by boosting immune function, and we consider whether physical activity could improve immunotherapy outcomes in age-related conditions such as cancer.

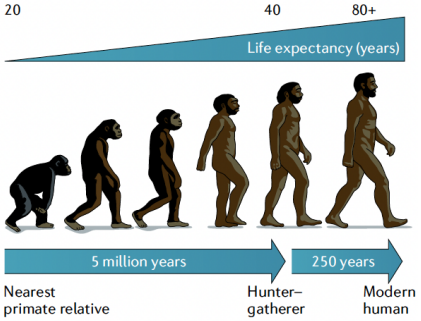


Fig. 1 | **The evolution of increased longevity.** Our nearest primate relatives, such as chimpanzees and gorillas, live for approximately 10–15 years in the wild once they reach maturity. Five million years of evolution resulted in a doubling of life expectancy in hunter–gatherer tribes such as the Ache and Hiwi, and this lifespan persisted into modern, 18th-century humans. Just 250 years later, as a result of improved sanitation and health care, life expectancy has doubled again[4], and our modern, more sedentary lifestyle is thus maladjusted to our genetic inheritance, with consequences for health in old age.

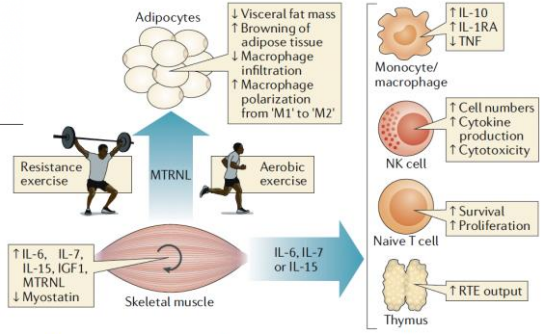


Fig. 2 | **Muscle as an immune regulatory organ.** In the absence of infection, skeletal muscle is a major source of cytokines, termed myokines. Active muscle produces a range of myokines, including IL-6, which has anti-inflammatory actions via the induction of IL-10 and IL-1 receptor antagonist (IL-1RA) by monocytes and macrophages. Muscle-derived IL-15 has a range of actions, including prompting the survival of naive T cells, enhancing natural killer (NK) cell production and cytotoxicity and influencing fat deposition by inhibition of lipogenesis. IL-7 has thymoprotective actions that help maintain thymic output. Skeletal muscle also produces a range of growth factors, including insulin-like growth factor 1 (IGF1) and Meteorin-like (MTRNL), which promotes the conversion of white to brown adipose tissue, increases in IL-4 secretion and macrophage M2 polarization. Increased physical activity leads to reduced intermuscular adipose tissue, which is a source of the inhibitory muscle growth factor myostatin. RTE, recent thymic emigrant; TNF, tumour necrosis factor.

Exercise & cancer (1):

official recommendations

Recommendation: *"Oncology providers should recommend regular aerobic and resistance exercise during active treatment with curative intent"*

CA CANCER J CLIN 2019;69:468–484

Exercise Is Medicine in Oncology: Engaging Clinicians to Help Patients Move Through Cancer

Kathryn H. Schmitz, PhD, MPH [1]; Anna M. Campbell, PhD [2]; Martijn M. Stuiver, PT, PhD [3,4,5]; Bernardine M. Pinto, PhD[6]; Anna L. Schwartz, PhD[7]; G. Stephen Morris, PT, PhD[8]; Jennifer A. Ligibel, MD[9]; Andrea Cheville, MD[10]; Daniel A. Galvão, PhD [11]; Catherine M. Alfano, PhD [12]; Alpa V. Patel, PhD[13]; Trisha Hue, PhD[14]; Lynn H. Gerber, MD [15]; Robert Sallis, MD[16]; Niraj J. Gusani, MD, MS [17]; Nicole L. Stout, PT, PhD[18]; Leighton Chan, MD, PhD[18]; Fiona Flowers, BS[19]; Colleen Doyle, MS, RD[20]; Susan Helmrich, PhD[21]; William Bain, PhD[22]; Jonas Sokolof, DO[23]; Kerri M. Winters-Stone, PhD [24]; Kristin L. Campbell, BSc, PT, PhD [25]; Charles E. Matthews, PhD [26]

ASCO special articles

Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline

Jennifer A. Ligibel, MD[1]; Kari Bohlke, ScD[2]; Anne M. May, PhD[3]; Steven K. Clinton, MD, PhD[4]; Wendy Demark-Wahnefried, PhD, RD[5]; Susan C. Gilchrist, MD, MS[6]; Melinda L. Irwin, PhD, MPH[7]; Michele Late[8]; Sami Mansfield, BA[9]; Timothy F. Marshall, PhD, MS[10]; Jeffrey A. Meyerhardt, MD, MPH[1]; Cynthia A. Thomson, PhD, RD[11]; William A. Wood, MD, MPH[12]; and Catherine M. Alfano, PhD[13]

abstract

PURPOSE To provide guidance on exercise, diet, and weight management during active cancer treatment in adults.

METHODS A systematic review of the literature identified systematic reviews and randomized controlled trials evaluating the impact of aerobic and resistance exercise, specific diets and foods, and intentional weight loss and avoidance of weight gain in adults during cancer treatment, on quality of life, treatment toxicity, and cancer control. PubMed and the Cochrane Library were searched from January 2000 to May 2021. ASCO convened an Expert Panel to review the evidence and formulate recommendations.

RESULTS The evidence base consisted of 52 systematic reviews (42 for exercise, nine for diet, and one for weight management), and an additional 23 randomized controlled trials. The most commonly studied types of cancer were breast, prostate, lung, and colorectal. Exercise during cancer treatment led to improvements in cardiorespiratory fitness, strength, fatigue, and other patient-reported outcomes. Preoperative exercise in patients with lung cancer led to a reduction in postoperative length of hospital stay and complications. Neutropenic diets did not decrease risk of infection during cancer treatment.

RECOMMENDATIONS Oncology providers should recommend regular aerobic and resistance exercise during active treatment with curative intent and may recommend preoperative exercise for patients undergoing surgery for lung cancer. Neutropenic diets are not recommended to prevent infection in patients with cancer during active treatment. Evidence for other dietary and weight loss interventions during cancer treatment was very limited. The guideline discusses special considerations, such as exercise in individuals with advanced cancer, and highlights the critical need for more research in this area, particularly regarding diet and weight loss interventions during cancer treatment.

Additional information is available at www.asco.org/supportive-care-guidelines.

Clin Oncol 40:2491-2507. © 2022 by American Society of Clinical Oncology

Exercise & cancer (2):

Exercise has a protective effect in many organs

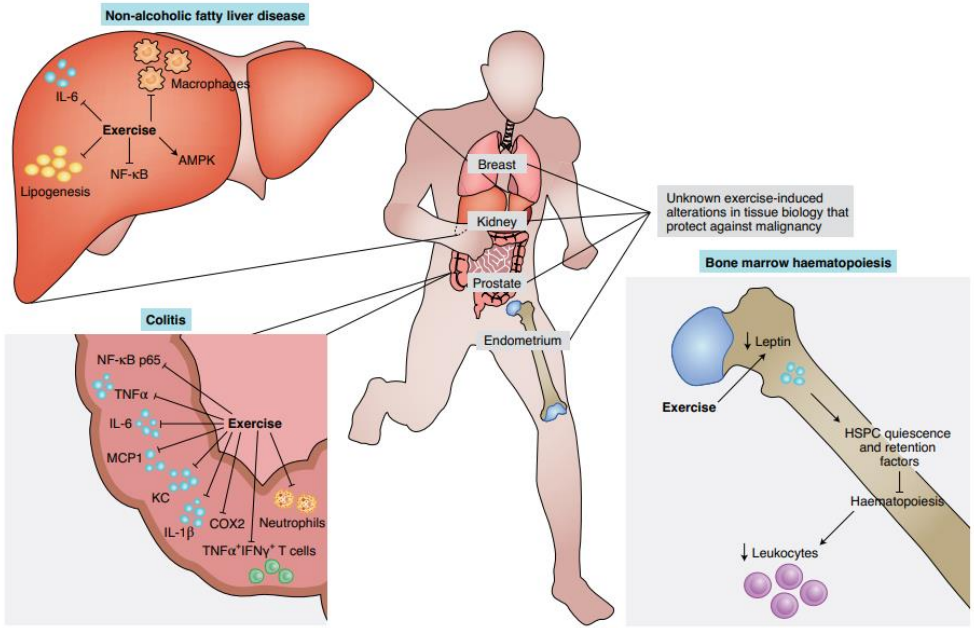


Fig. 1 | Exercise-induced protection against tissue-specific perturbations in organs involved in cancer regulation or prone to malignancy. Blue boxes contain illustrative examples of the liver, colon and bone marrow. Grey boxes indicate examples of tissues in which data supporting exercise-induced regulation of tissue biology in the absence of frank malignancy are currently lacking. KC, keratinocyte chemoattractant; COX2, cyclooxygenase-2.

Koelwijn *et al.* Nat Met 2022

Exercise & cancer (3):

Exercise induces a strong immune & metabolic remodeling

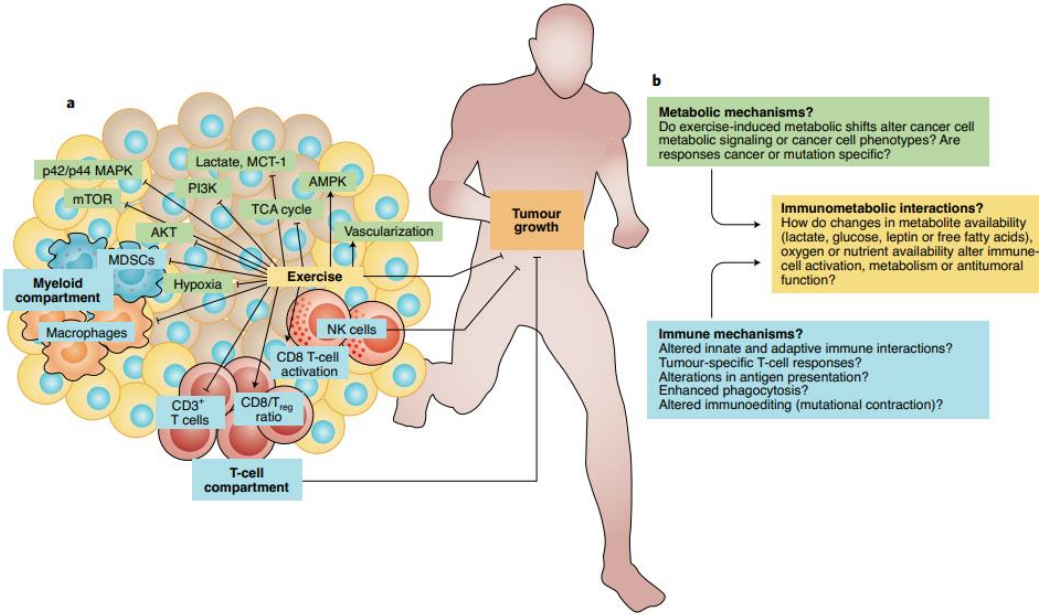
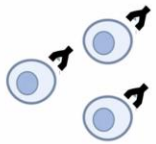
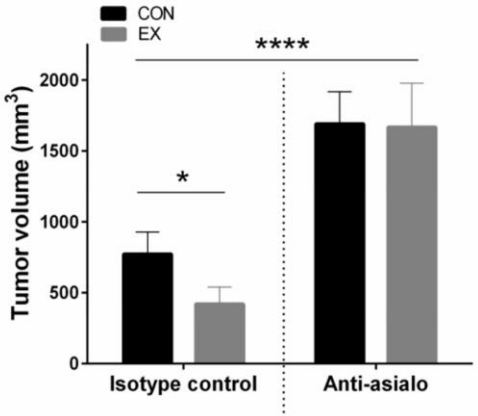


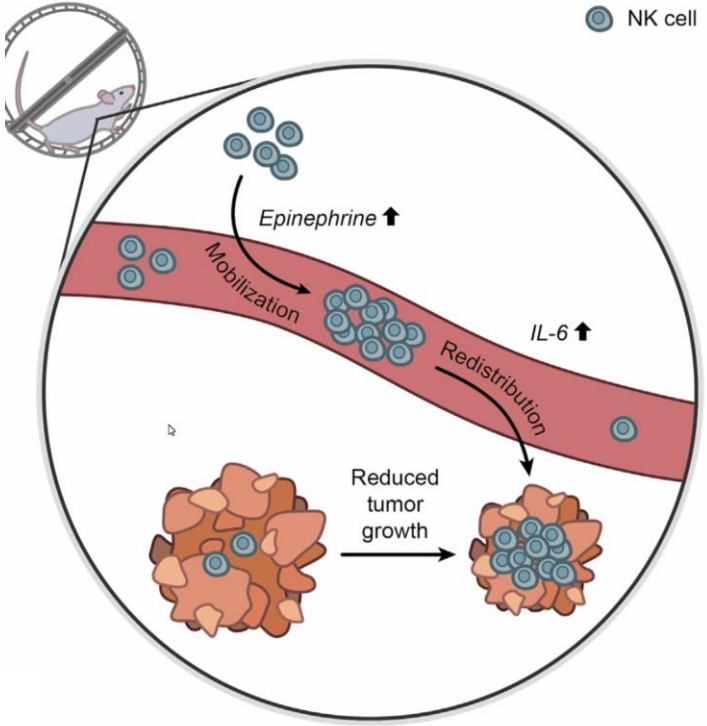
Fig. 2 | Exercise-induced regulation of immunological and metabolic function in the TME. a, Exercise alters the immunological composition of the TME (blue boxes), decreasing the proportion of innate immune cell populations (macrophages and MDSCs) and increasing $CD3^+$ T cells and NK cells. Furthermore, the ratio of $CD8^+$ T cells versus regulatory T cells (T_{reg}), as well as the activation of $CD8^+$ T cells ($CD69^+$), increases with exercise. Exercise

Koelwijn *et al.* Nat Met 2022

Depletion of NK cells completely abolishes the effect of exercise on tumor growth

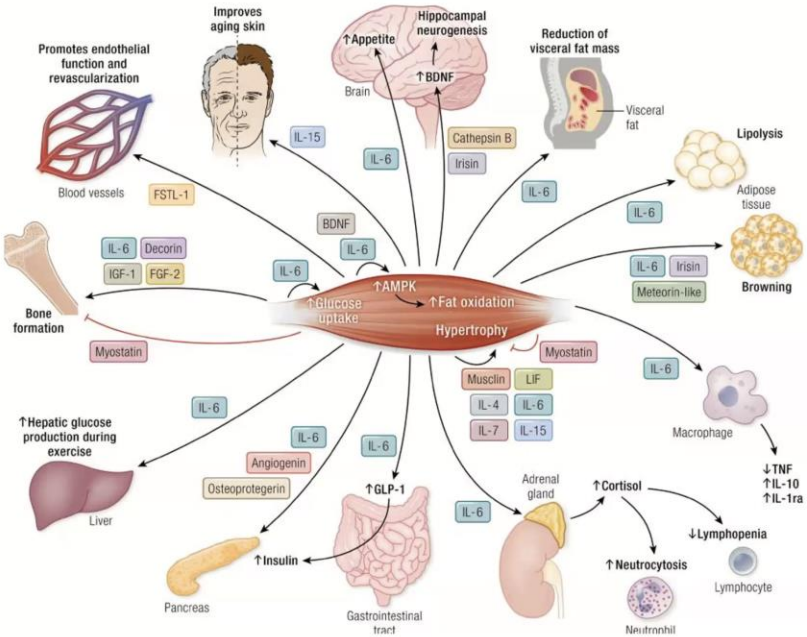


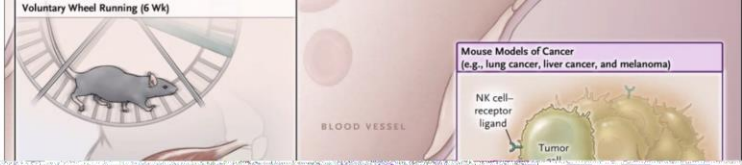


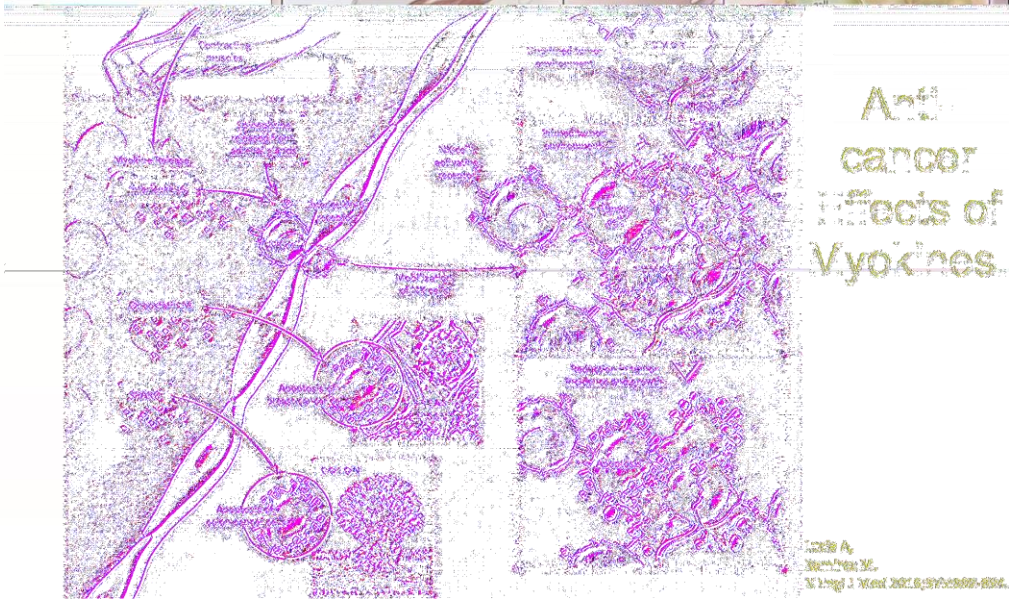


Pedersen, L. et al, Cell Metab 2016

Cell Metabolism February 2016







Severinsen MCK, Pedersen BK. Muscle-Organ Crosstalk: The Emerging Roles of Myokines. Endocr Rev. 2020;41(4):594-609.

Table 1 | Ongoing clinical trials of structured exercise therapy in cancer prevention and prognosis

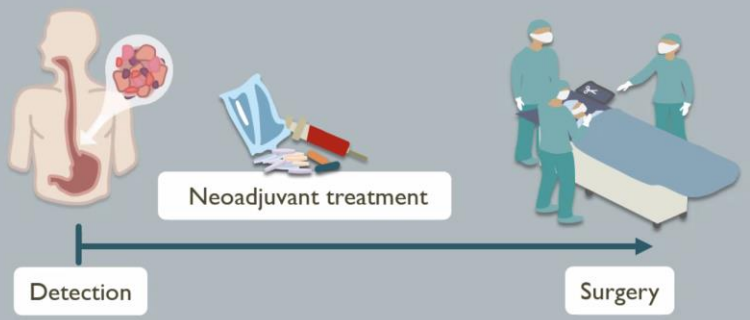
Trial	Design	ClinicalTrials.gov identifier	Sample size and population	Exercise intervention	Cancer-specific endpoints
Post-diagnosis: phase 3 trials					
Intense Exercise for Survival Among Men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL)[85]	Phase 3 RCT	NCT02730338	866 patients with advanced prostate cancer	2 years: individualized, progressive moderate- to high-intensity aerobic and resistance exercise, supervised (year 1) and home based (year 2)	Primary: overall survival Secondary: disease progression, program safety
Colon Health and Life-Long Exercise Change (CHALLENGE)[86]	Phase 3 RCT	NCT00819208	962 patients with stage II/III colon cancer	3 years: combined behaviour support with supervised or unsupervised activity sessions with the goal of increasing recreational physical activity up to 27 metabolic-equivalent hours per week	Primary: disease-free survival Secondary: overall survival
Post-diagnosis: other trials					
Effect of Physical Exercise on Tumour Proliferation of Luminal B Breast Cancer Patients (EFIK)	Case–control	NCT03860740	60 patients with operable and untreated HR^+HER2^- breast cancer	2–3 weeks before surgery: 60–100% VO_{2peak} for 10 sessions minimum	Primary: tumour proliferation (Ki-67), proliferation score (PAM50) Secondary: change from baseline molecular subtypes (PAM50), intratumoural VEGF, HIF-1, cleaved caspase-3
Exercise Treatment with Standard Therapy for Metastatic Breast Cancer	Phase 1a/b	NCT03988595	60 patients with HR^+ metastatic breast cancer	24 weeks: 3–5× per week, with four escalated doses of 90, 150, 225 or 300 minutes per week	Phase 1a (dose escalation): Primary: maximum feasible dose Secondary: change in circulating tumour DNA, tumour proliferation (Ki-67), HR signalling Phase 1b (dose expansion): Primary: change in circulating tumour DNA Secondary: tumour proliferation (Ki-67), HR signalling
Exercise Interventions for Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy (BENEFIT)	3-arm RCT	NCT02999074	240 patients with breast cancer, scheduled for neoadjuvant chemotherapy	18 weeks: 2 interventions of resistance exercise (2× week) comprising 8 machine-based exercises, each performed in 3 sets of 12 repetitions at 60–80% of one repetition maximum or aerobic exercise (2× per week) at up to 60–70% VO_{2peak}	Primary: tumour size, as change from baseline (before start of neoadjuvant chemotherapy) to breast surgery Secondary: CPS-EG score, pathological complete response
A Study of the Body's Response to Exercise and a Plant-Based Diet in Overweight Postmenopausal Women with Breast Cancer	2-arm RCT	NCT04298086	62 patients with HR^+HER2^- stage I–III breast cancer, receiving aromatase inhibitor	24 weeks: 7× per week to achieve the patient-specific goal energy expenditure in conjunction with a plant-based diet	Primary: change in breast aromatase levels Secondary: change in breast-tissue gene expression
Study of the Effects of Pre-surgical Aerobic Exercise on Patients with Solid Tumors	Phase 0 or 1a/b	NCT03813615	78 patients with phase 0 early-stage breast, endometrial or prostate cancer, or phase 1a/b operable, untreated prostate cancer	Phase 0: >2 weeks of aerobic training for 150 minutes per week, 5× per week Phase 1a: >2 weeks of aerobic training for 150, 225, 300 or 375 minutes per week, 3–6× per week Phase 1b: dose expansion	Phase 1a. Maximal feasible dose with biological activity Phase 1b. further examination of tolerability and activity
Prevention					
Physical Activity, Proliferation and Immune Markers in Benign Breast Tissue	Single arm	NCT03657628	60 premenopausal women with high breast density	12 weeks: supervised, moderate-intensity aerobic exercise	Primary: proliferation (Ki-67)
Dose-Response of Aerobic Training in Women at High-Risk for Development of Breast Cancer	3-arm RCT	NCT02494869	75 women at high risk of breast cancer (family history, atypical hyperplasia)	24 weeks with 2 exercise doses: either 150 minutes per week of aerobic training (3× for 50 minutes) at 55–100% VO_{2peak} or 300 minutes per week of aerobic training (5× for 60 minutes) at 55–100% VO_{2peak}	Primary: changes in gene expression patterns of non-neoplastic breast epithelial cells Secondary: changes in genomic or epigenomic profiles

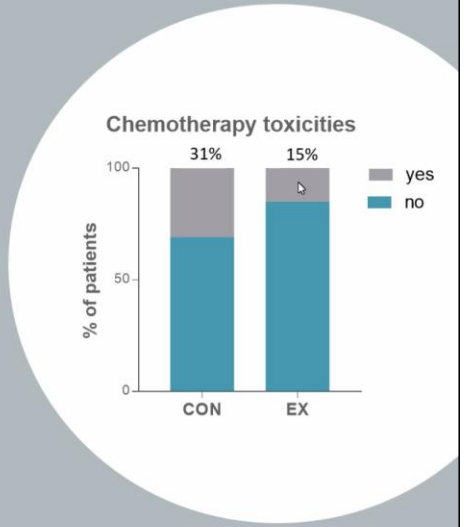
HR: hormone receptor; HER2: human epidermal growth factor receptor 2; VO_{2peak}: peak rate of oxygen consumption; CPS-EG: Clinical-Pathologic Stage score.

Several randomized clinical trials ongoing to prevent cancer or cancer recurrence.

Koelwijn *et al.* Nat Met 2022

Exercise training reduces the toxicities to neoadjuvant chemotherapy



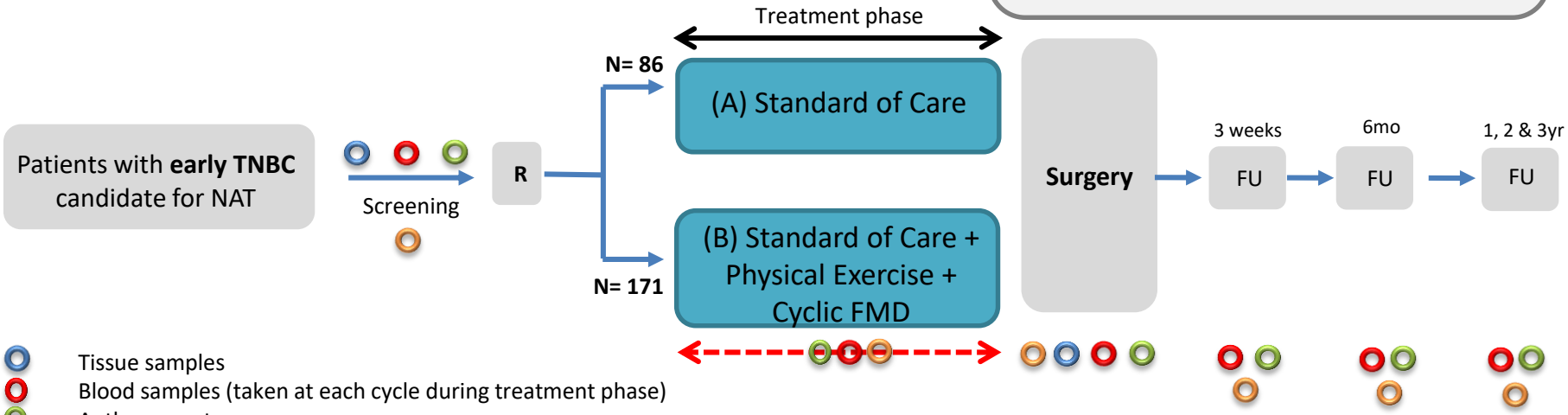


Christensen et al, BJS Open 2018

LESLIE: study design

Prof. Christine Desmedt KU Leuven

PIs: C. Desmedt/A. Smeets (UZ/KU Leuven)
Co-PIs: C. Fontaine (UZ Brussels), A. Prové (GZA), W. Tjalma (UZA), E. Naert (UZ Ghent)
Proj. managers: M. Maetens, H. Vos
Study biostatistician: Elia Biganzoli (Uni. Milan)



Tissue samples
Blood samples (taken at each cycle during treatment phase)
Anthropometry measures
Questionnaires: dietary intake, physical activity, fatigue and quality of life (QoL)

Abbreviations: FMD: fast-mimicking diet; mo: Month; N: Number of patients; NAT: neoadjuvant therapy; R: Randomization; TNBC: Triple negative breast cancer; yr: Year; FU: Follow-up

Combination of FMD and exercise

- Both FMD and exercise have been demonstrated to have the potential to increase efficacy and tolerability of cancer treatments.
- Exercise helps to preserve muscle mass, strength and phase angle during FMD-therapy.
- Synergistic effects of both interventions demonstrated in rodents.

Objectives

- Primary objective: pathological response
- Secondary objectives: survival, health-related quality of life, body composition, side-effects, neoadjuvant therapy compliance

Xie *et al.* J Biol Chem 2007, Valdemarin et al. Cancers 2021, Bauersfeld *et al.* BMC Cancer 2018

PD12-08 Randomized trial of exercise and nutrition on pathological complete response among women with breast cancer receiving neoadjuvant chemotherapy: the Lifestyle, Exercise and Nutrition Early after Diagnosis (LEANer) Study

Thursday, December 8, 2022
7:00 AM - 8:15 AM
Room: Hemisfair Ballroom 1&2

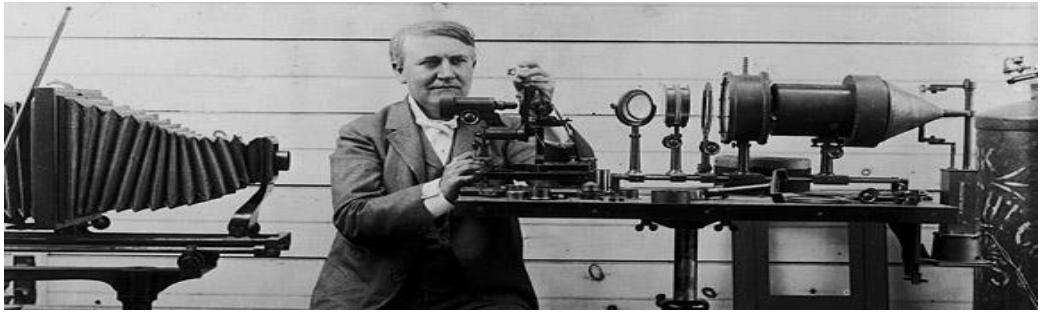
Leah Ferrucci, PhD, MPH - Yale School of Public Health
Tara B. Sanft, MD - Yale School of Medicine
Maura Harrigan, MS, RDN, CSO - Yale School of Public Health
Brenda Cartmel, PhD - Yale School of Public Health
Fangyong Li, MS, MPH - Yale School of Medicine
Michelle Zupa, n/a - Yale Cancer Center
Courtney McGowan, RD - Yale School of Public Health
Leah Puklin, MPH - Yale School of Public Health
Thai Hien Nguyen, MPH - Yale School of Public Health
Anna M. Tanasijevic, MPH - Dana-Farber Cancer Institute
Marian L. Neuhouser, n/a - Fred Hutchinson Cancer Center
Dawn Hershman, MD, MS, FASCO - Columbia University
Karen Basen-Engquist, PhD, MPH - MD Anderson Cancer Center
Beth Jones, PhD, MPH - Yale School of Public Health
Tish Knobf, PhD, RN, FAAN - Yale School of Nursing
Anees B. Chagpar, MD, MSc, MPH, MA, MBA - Yale University
Andrea L.M. Silber, n/a - Yale University
Jennifer A. Ligibel, MD - Dana-Farber Cancer Institute
Melinda L. Irwin, PhD, MPH - Yale School of Public Health

Methods: The Lifestyle, Exercise and Nutrition Early after Diagnosis (LEANer) Study enrolled 173 women with Stage I-III breast cancer who were randomized to usual care (n = 86) or a yearlong, 16-session, in-person or telephone-administered diet and physical activity intervention (n = 87) delivered by registered dietitians. Among study participants, 73 women received neoadjuvant chemotherapy and of these, 72 (98.6%) had complete follow-up pCR data (intervention = 40; usual care = 32). pCR, dates, doses and reason for dose-adjustments/delays of chemotherapy were abstracted from electronic medical records and confirmed with treating oncologists. A Chi-square test was used to examine the effect of the intervention versus usual care on pCR.

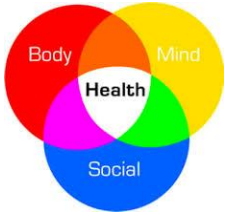
Conclusions: A primarily telephone-based diet and physical activity intervention led to improved pCR compared to usual care among the subset of women with breast cancer in the LEANer Study who received neoadjuvant chemotherapy. As pCR is an important prognostic factor for breast cancer, additional lifestyle interventions focusing on the neoadjuvant treatment setting with pCR as the primary outcome are necessary to confirm the potential benefits of lifestyle changes on pCR.

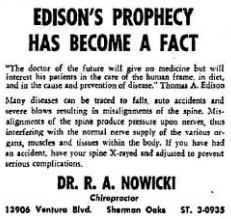
The doctor of the future will give no medicine, but instead will interest his patients in the care of human frame, in diet, and in the cause and prevention of disease.

Thomas Edison (1847 – 1931)



("Wizard Edison" in *The Newark Advocate* (2 January 1903), p. 1)





EDISON'S PROPHECY HAS BECOME A FACT

"The doctor of the future will give no medicine but will interest his patients in the care of the human frame, in diet, and in the cause and prevention of disease." Thomas A. Edison

Many diseases can be traced to falls, auto accidents and severe blows resulting in misalignments of the spine. Misalignments of the spine produce pressure upon nerves, thus interfering with the normal nerve supply of the various organs, muscles and tissues within the body. If you have had an accident, have your spine X-rayed and adjusted to prevent serious complications.

DR. R. A. NOWICKI
Chiropractor
13906 Ventura Blvd. Sherman Oaks ST. 3-0935

From Precision Medicine to Precision Healthcare

Cell
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Review

Hallmarks of Health

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[2]Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain
[3]Centro de Investigacion Biomedica en Red de Cancer (CIBERONC), Madrid, Spain
[4]Centre de Recherche des Cordeliers, Equipe labellisée par la Ligue contre le cancer, Université de Paris, Sorbonne Université, INSERM U1138, Institut Universitaire de France, Paris, France
[5]Metabolomics and Cell Biology Platforms, Gustave Roussy, Villejuif, France
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[7]Suzhou Institute for Systems Medicine, Chinese Academy of Medical Sciences, Suzhou, China
[8]Karolinska Institute, Department of Women's and Children's Health, Karolinska University Hospital, Stockholm, Sweden
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https://doi.org/10.1016/j.cell.2020.11.034

SUMMARY

Health is usually defined as the absence of pathology. Here, we endeavor to define health as a compendium of organizational and dynamic features that maintain physiology. The biological causes or hallmarks of health include features of spatial compartmentalization (integrity of barriers and containment of local perturbations), maintenance of homeostasis over time (recycling and turnover, integration of circuitries, and rhythmic oscillations), and an array of adequate responses to stress (homeostatic resilience, hormetic regulation, and repair and regeneration). Disruption of any of these interlocked features is broadly pathogenic, causing an acute or progressive derailment of the system coupled to the loss of numerous stigmata of health.

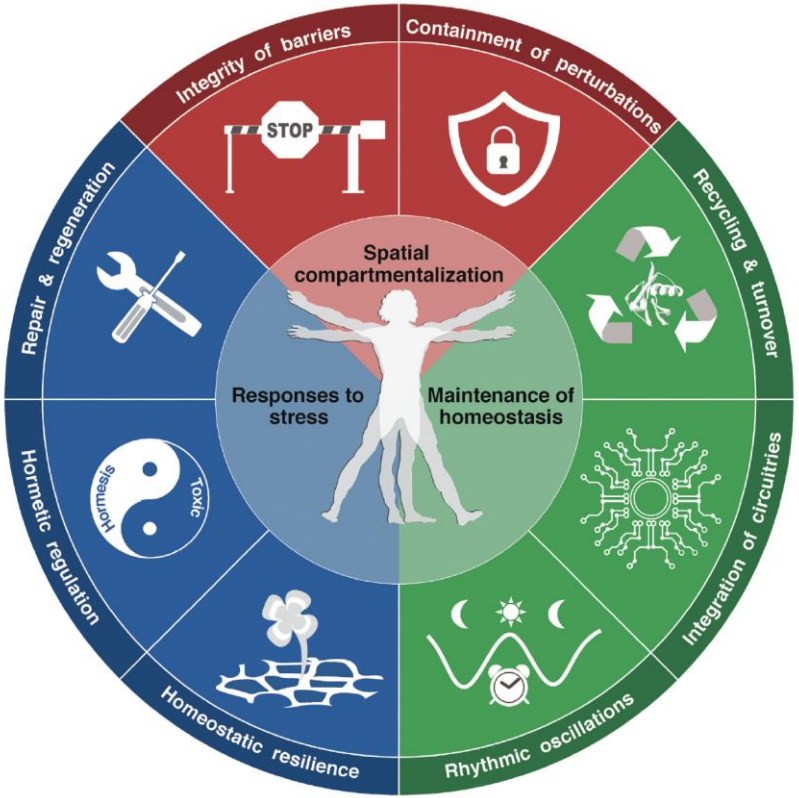

Figure 1. The Hallmarks of Health
The scheme compiles the eight hallmarks of health proposed in this review: integrity of barriers, containment of local perturbations, recycling and turnover, integration of circuitries, rhythmic oscillations, homeostatic resilience, hormetic regulation, and repair and regeneration. These hallmarks are grouped into three categories: spatial compartmentalization, maintenance of homeostasis over time, and adequate responses to stress.

JNCI: Journal of the National Cancer Institute, 2023, 115(1), 43–51
https://doi.org/10.1093/jnci/djac192
Advance Access Publication Date: 10 October 2022
Article

Childhood body mass index trajectories, adult-onset type 2 diabetes, and obesity-related cancers

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Abstract

Background: Elevated childhood body mass index (BMI), commonly examined as a "once-only" value, increases the risk of cancer and type 2 diabetes (T2D) in adulthood. Continuous exposure to adiposity during childhood may further increase cancer risk. We examined whether longitudinal childhood BMI trajectories were associated with adult obesity-related cancer and the role of adult-onset T2D in these associations.

Methods: Five sex-specific latent class BMI trajectories were generated for 301 927 children (149 325 girls) aged 6-15 years from the Copenhagen School Health Records Register. Information on obesity-related cancers and T2D was obtained from national health registers. Incidence rate ratios (IRR), cumulative incidences, and confidence intervals (CI) were estimated using Poisson regressions.

Results: Compared with the average childhood BMI trajectory (containing approximately 40% of individuals), the rate of obesity-related cancer (excluding breast cancer) increased with higher childhood BMI trajectories among women. The highest rates occurred in the overweight (IRR = 1.27, 95% CI = 1.17 to 1.38) and obesity (IRR = 1.79, 95% CI = 1.53 to 2.08) BMI trajectories. Similar patterns were observed among men. In contrast, women with the obesity childhood BMI trajectory had the lowest rate of pre- and postmenopausal breast cancer (IRR = 0.59, 95% CI = 0.43 to 0.80, and IRR = 0.41, 95% CI = 0.30 to 0.57, respectively). For all trajectories, the cumulative risk of obesity-related cancer increased with adult-onset T2D.

Conclusion: Consistent childhood overweight or obesity may increase the rates of adult obesity-related cancer and decrease the rates of breast cancer. Adult-onset T2D conferred additional risk for obesity-related cancer, but the effect did not differ across childhood BMI trajectories.

Network UNIMI GSA(PNRR) LS 8 - Inflammaging

HEBE Project

Healthy aeging versus inflamm-aeging:

the role of physical Exercise

in modulating the Biomarkers

of age-associated and Environmentally determined chronic diseases

HEBE Web

https://hebe.unimi.it

Home » Vivere in salute

Vivere in salute

In questa sezione troverai informazioni e consigli utili per seguire un corretto stile di vita, migliorando la tua salute e riducendo il rischio di patologie.
Queste semplici indicazioni sono affrontate con un approccio scientifico sulla base dei più recenti studi e delle indicazioni dei più importanti Enti e Società medico-scientifiche nazionali ed internazionali. Un cambiamento nello stile di vita ha ricadute positive su benessere, qualità della vita e salute... e allora che cosa aspetti?

Troverai 4 sezioni, alle quali puoi accedere direttamente in fondo a questa pagina: "attività fisica", "alimentazione", "benessere psicofisico" e "misura la tua salute".

MISURA LA TUA SALUTE

Quali domande ti devi fare per capire se sei in salute

I più moderni approcci alla valutazione dello stato di salute si basano sia su test clinici che su aspetti legati allo stile di vita. Questo tipo di valutazione predilige mettere...

LEGGI TUTTO →

ALIMENTAZIONE, VIVERE IN SALUTE

Principi generali per un'alimentazione corretta

Dal punto di vista di una prevenzione primaria (azioni sulla popolazione generale per evitare o ridurre, a monte, l'insorgenza e lo sviluppo di una malattia) o secondaria (diagnosi precoce di...

LEGGI TUTTO →

ATTIVITÀ FISICA, VIVERE IN SALUTE

Attività fisica: come quando e perché

Sebbene tutti sappiano che l'attività fisica fa bene, sono pochi coloro che si possono ritenere realmente attivi. Perché? "non ho tempo!" "sono troppo stanco!" "non so cosa devo fare" sono tra...

LEGGI TUTTO →

HEBE a SuperQuark

Il 17 agosto 2022 è andato in onda su Rai1 il servizio di SuperQuark
«Camminare fa bene»
con la consulenza scientifica dei ricercatori di HEBE,
girato negli studi e laboratori della Statale dove svolgono la loro ricerca

- *Sul canale YouTube Rai1 più di 900 mila visualizzazioni, 10 mila like, 400 commenti*

Che sia benedetta

Per quanto assurda e complessa ci sembri la vita è perfetta

Per quanto sembri incoerente e testarda se cadi ti aspetta

E siamo noi che dovremmo imparare a tenercela stretta

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