Published OnlineFirst July 7, 2016; DOI: 10.1158/1055-9965.EPI-16-0223

Minireview

Cancer Epidemiology, Biomarkers & Prevention

Exercise and Prostate Cancer: Evidence and Proposed Mechanisms for Disease Modification

Brian D. Hayes[1,2], Lauren Brady[2], Michael Pollak[3], and Stephen P. Finn[2,4]

Abstract

Exercise has many potential benefits in relation to cancer. Apart from primary prevention, these include improvement of nonspecific cancer-related symptoms, amelioration of symptoms and cardiovascular risk factors related to cancer treatment, and improvements in various quality-of-life–related factors. Increasing evidence also points toward improved cancer-free and overall survival in cancer patients who undertake regular exercise, findings which should encourage further research in this area. Obesity is known to be associated with a proinflammatory, prothrombotic humoral milieu, which may promote aggressiveness in prostate cancer through interactions with NK-cell–mediated killing of circulating tumor cells, through platelet-circulating tumor cell interactions, and through alterations in adipokine and myokine profile among others. Physical activity reduces levels of systemic inflammatory mediators and so exercise may represent an accessible and cost-effective means of ameliorating the proinflammatory effects of obesity in cancer patients. This review outlines the evidence for the benefits of exercise in these patients, focusing on prostate cancer, and delineates current theories of the underlying biological mechanisms. *Cancer Epidemiol Biomarkers Prev; 25(9); 1281–8. ©2016 AACR.*

Introduction

Prostate cancer, the most frequently diagnosed male cancer in the developed world (1), is a leading cause of male cancer–related death. Although prostate-specific antigen (PSA) screening identifies many early cancers, numerous men still present with locally advanced or metastatic disease for whom radical surgery with curative intent is inappropriate. In this setting, increased disease-free and overall survival and improved quality-of-life (QoL) are the primary management objectives, and new therapies and lifestyle alterations that can assist are increasingly needed.

Exercise has well-documented benefits in improving cardiovascular risk and bone mineral density and in treating obesity and diabetes. The incorporation of exercise programs into cancer care is increasingly recognized to have beneficial effects. A systematic review of exercise interventions in cancer survivors found improvements in strength, fatigue, fitness, functional QoL, self-esteem, and anxiety (2). Much of this research relates to colon and breast cancer but increasing evidence demonstrates improvements in symptom control, all-cause mortality, and cancer-specific mortality in prostate cancer also. Improved cancer-specific mortality suggests the potential for exciting developments in our understanding of the biology and aggressiveness of prostate cancer, together with novel therapeutic opportunities.

In prostate cancer patients with potentially curable disease, obesity and its complications may make surgery impractical. Androgen deprivation therapy (ADT), the mainstay of systemic treatment for hormone-responsive advanced prostate cancer, itself causes obesity and metabolic syndrome. As medical therapy for obesity-related cardiovascular risk factors improves, aggressiveness of prostate cancer becomes more important than cardiovascular complications in determining the cause of mortality in these men. We know that obese men have a worse outlook regarding cancer-related mortality than nonobese men. The combination of an aging population with an increased prostate cancer incidence, increasing obesity prevalence, and improved management of cardiovascular risk factors means that in the future more men are going to die as a result of the deleterious effect of overweight in advanced prostate cancer.

This review will attempt to outline the observational and experimental evidence for the benefits of exercise in prostate cancer patients with particular reference to the amelioration of the negative effects of obesity. It will also delineate the current theories as to the biological mechanisms underlying these benefits.

Evidence for Benefits of Exercise in Cancer Patients

Cancer and benefits of exercise

Regular exercise is important for primary prevention of many cancers. It is associated with decreased risk of endometrial (3), colon (4), bladder (5), renal (6), gastroesophageal (7), and breast cancers, with a dose–effect relationship in the latter in some studies (8). Evidence for exercise in reduction of hematologic cancer risk is not convincing (9).

Exercise helps ameliorate nonspecific cancer-related symptoms, reduces cardiovascular risk factors (10), and improves general QoL, even without reduction in body weight. A meta-analysis (11) found moderately reduced cancer-related fatigue

[1]Department of Histopathology, Cork University Hospital, Wilton, Cork, Ireland. [2]Department of Histopathology & Morbid Anatomy, Trinity College, Dublin, Ireland. [3]Departments of Medicine and Oncology, McGill University, Montreal, Quebec, Canada. [4]Department of Histopathology, St. James's Hospital, Dublin, Ireland.

Corresponding Author: Brian D. Hayes, Department of Histopathology, Cork University Hospital, Wilton, Cork, Ireland. Phone: +353-21-492-2523; Fax: +353-21-492-2774; E-mail: hayesb3@tcd.ie

doi: 10.1158/1055-9965.EPI-16-0223

Published OnlineFirst July 7, 2016; DOI: 10.1158/1055-9965.EPI-16-0223

and improved symptoms of depression and sleep disturbance. A Cochrane review (12) found that "aerobic exercise can be regarded as beneficial for individuals with cancer-related fatigue during and post-cancer therapy". A separate Cochrane review (13) found improvements in body image/self-esteem, sexuality, social functioning, anxiety, and pain. These QoL indicators are particularly important in patients with advanced cancers for whom treatment with the aim of cure is inappropriate.

The emerging evidence for improved cancer-specific overall and progression-free survival in exercise therapy is exciting. While the potential benefits should not be overstated, exercise is increasingly considered an anticancer therapy in its own right. A systematic review found improved outcomes in breast and colon cancer (14), although no randomized controlled trials are available. The evidence includes the benefits of post-diagnosis physical activity (15) as well as long-term exercise participation before breast cancer diagnosis (16). Similarly, in colon cancer, there is evidence for both pre- (17) and post-diagnosis (18, 19) exercise. A supervised exercise program may be associated with improved progression-free survival in lymphoma (20).

Prostate cancer and benefits of exercise

Prostate cancer is a heterogenous disease, and risk factor associations for total nonaggressive disease are different from aggressive/lethal disease (21). A retrospective questionnaire-based study of 988 cancer patients (T2 or greater) and 1,063 controls found that vigorous physical activity and physical activity over the first 18 years of life decreased cancer risk (22). A large prospective study found no association between occupational or leisure time activity and prostate cancer incidence (23), although occupational activity was associated with lower risks of advanced-stage prostate cancer. In the Health Professionals Follow-up Study (24), there was a lower risk of advanced, high Gleason grade, or fatal prostate cancer in men over 65 years of age undertaking the highest category of vigorous activity. There was no association with prostate cancer incidence for total, vigorous, and nonvigorous activity overall. Most other population-based studies show similar findings, with little effect of exercise on overall incidence but some association with reduced aggressive cancers (25–27). Some studies find increased risk of prostate cancer in selected groups of men undertaking exercise (28, 29), which underlines the complexity of the issues involved and the difficulty in controlling for quantity and type of exercise in large-scale observational studies.

The diagnosis of prostate cancer may provide a "teachable moment" when men are amenable to lifestyle changes. For prostate cancer patients, in whom most exercise studies assess QoL indicators, there is solid evidence that exercise (especially group exercise) improves muscular and aerobic endurance, reduces fatigue, and improves overall QoL (30). There is relatively strong evidence for improved health-related, social, and physical QoL. Exercise has specific benefits in ameliorating prostate cancer treatment side-effects, such as improved muscular strength, cardiorespiratory fitness, lean body mass, and fatigue (31). Among 66 men undergoing radiotherapy, there was significantly reduced rectal toxicity after 30 minutes of aerobic walking exercise, three times per week, for 4 weeks (32). Among 121 men receiving radiotherapy and/or androgen blockade, both resistance and aerobic exercise improved fatigue, and resistance exercise also improved QoL, strength, triglycerides, and body fat (33). Another study found significant changes in waist circumference following a 16-week intervention, although with high drop-out rates (34).

Accumulating data suggest that exercise can modify the biology of prostate cancer, in addition to improving QoL-related parameters. In a follow-up study of 2,705 men with nonmetastatic prostate cancer who survived at least 4 years after diagnosis, vigorous exercise (cycling, swimming, jogging) for more than 3 hours weekly led to lower all-cause and cancer-specific mortality (35). Brisk walking trended towards lower cancer-specific mortality without achieving statistical significance. Another study found 57% reduced progression rates among men with clinically localized prostate cancer who walked briskly for more than 3 hours weekly. Walking pace was associated with decreased risk of progression independent of duration (36). Several more recent large follow-up studies provide further evidence for physical activity in reducing prostate cancer–specific mortality (37, 38).

Feasibility of exercise programs in cancer patients

The quality of clinical evidence for exercise programs in advanced cancer is somewhat limited by difficult accrual of participants to trials. Individual studies should be assessed critically, as the ability to undertake exercise may act as a surrogate for better performance status, which may in turn act as confounding factor. Supervised exercise programs are feasible in colon (39) and even posttreatment lung cancer (40). The PEACH trial (41) recruited a heterogeneous sample of cancer survivors for a supervised exercise intervention: 186 patients were available for recruitment, 43 (23%) of whom were randomized into the program. A common reason for exclusion was a potential participant residing too far from the study site, suggesting that recruitment from multiple clinical sites may help to achieve accrual targets.

Many PEACH trial participants were breast cancer survivors, and had a younger age profile than would be expected for a prostate cancer study. Prostate cancer patients might be less inclined to participate in moderate-to-vigorous intensity exercise than younger breast cancer patients. However, Richman and colleagues' study (36) included many participants who engaged in regular walking at a brisk pace (34.5%). Kenfield and colleagues' study (35) shows improved mortality in those who exercised for >9 MET-h/week, with approximately 75% engaging in this level of activity. The Richman and colleagues study (36) supports the hypotheses that brisk walking may elicit the same physiologic responses as more vigorous exercise does in a different man, and that moderate-to-brisk intensity walking intervention may be acceptable to a considerable proportion of prostate cancer patients. An international multicenter trial of exercise in men with advanced prostate cancer (the ExPeCT trial; ClinicalTrials.gov identifier NCT02453139) is currently underway at our institution, and participant accrual targets are being met.

Potential Mechanisms

Metabolic syndrome and systemic inflammation

Metabolic syndrome is a constellation of cardiovascular disease risk factors, including hypertriglyceridemia, hypertension, and low HDL cholesterol, with central adiposity and insulin resistance

Published OnlineFirst July 7, 2016; DOI: 10.1158/1055-9965.EPI-16-0223

the most important components. In the United States, more than 30% of adults are obese (42). Hypogonadism, due to androgen deprivation therapy (ADT), the mainstay of treatment for advanced prostate cancer, is an independent risk factor for the components of metabolic syndrome (43–47). Fifty-percent of men undergoing long-term ADT have metabolic syndrome (48), possibly contributing to the excess noncancer mortality in this population (49). Obesity/metabolic syndrome is associated with progression but not incidence of prostate cancer (50). Overweight and high plasma C-peptide levels predispose to cancer-related death in men subsequently diagnosed with prostate cancer (51). However, evidence for metabolic syndrome as a risk factor in development of prostate cancer is inconclusive (52, 53).

Metabolic syndrome may promote prostate cancer aggressiveness through altered insulin-like growth factor (IGF) signaling. IGF1 binds to IGF1 receptor (IGF1R), and its function can be modulated by IGF-binding proteins (IGFBP). When activated IGF1R increases proliferative and antiapoptotic activity via the RAF and PI3K pathways (54). Metabolic syndrome–associated hyperinsulinemia appears to inhibit the modulatory function of IGFBP1, increasing the concentration of nonbound bioavailable IGF1 (55). In addition to this systemic effect, the local tumor environment also leads to increased sensitivity to IGF1 through increased expression of the IGF1R receptor. (56, 57).

Metabolic syndrome is characterized by low-level chronic systemic inflammation (reviewed in ref. 58), and evidence suggests that substantial crosstalk occurs between pathways involved in inflammation, coagulation, and obesity (59). Tissue factor (TF), the principal initiator of the coagulation cascade, is also a proinflammatory mediator, triggering signaling through G-protein–coupled receptors. TF appears to have a critical role at the crossroads of obesity, inflammation, and thrombosis (60). In mice, inhibited TF-mediated signaling in hematopoietic cells reduced high-fat diet–related insulin resistance (through downregulation of TNFα and IL6 and upregulation of IL10), without impacting body weight. In adipose tissue, inhibited TF-mediated signaling led to reduced weight gain. In a seminal article, TNFα was shown to be constitutively expressed in adipose tissue and hyperexpressed in obesity (61). Other inflammatory mediators (IL6, CRP, and MIF) are also increased in obese patients. IL6 and TNFα stimulate leptin and reduce adiponectin production, and TNFα suppresses NO synthase expression. Apart from its metabolic effects, insulin mediates many other processes, including platelet inhibition by increasing NO expression, anti-inflammatory activity by decreasing NFκB and CRP, and antithrombotic activity by reducing TF activity. In a rat model, rises in serum IL6 and TNFα were suppressed by insulin (62). Insulin resistance is characteristic of metabolic syndrome. Therefore, obese men tend to be in a proinflammatory and prothrombotic state.

There are substantial preclinical experimental data, both in prostate cancer cell culture studies and murine models, to support the hypothesis that reductions in systemic inflammatory mediators (with consequent effects on platelet adhesion) may underlie exercise-associated improved outcomes. Incubation with serum from healthy male volunteers after exercise led to 31% inhibition of growth of LNCaP prostate cancer cell lines, and preincubation of LNCaP cells before injection into immunodeficient mice led to delayed tumor formation (63). EGF and IGFBP1 may exert inhibitory effects on postexercise serum. A similar study using serum from men undergoing a low-fat, high-fiber diet in addition to regular exercise reduced growth and increased apoptosis in LNCaP cells, associated with reductions in serum IGF1 (64). The cells also had increased p53 content (replicated elsewhere; ref. 65) and reduced NF-κB activation. In a study of men with early-stage, low-grade prostate cancer who undertook comprehensive diet and lifestyle changes, it was found that their serum inhibited LNCaP cell growth more than the serum of a comparison group of men who did not make these changes (66). Mice injected with prostate cancer cells and randomized to voluntary exercise tended toward reduced expression of prometastatic genes, with no change in primary tumor growth rate (67). There was also improved tumor vascularization, modulated through increased HIF1α and VEGF concentrations leading to productive (nonpathologic) angiogenesis. In a separate SCID mouse xenograft model, voluntary running wheel exercise led to suppressed PC-3 tumor growth in male mice, manifested by reduced mitosis and increased apoptosis. The regimen was associated with increased food and fluid consumption by the mice and led to reduced adiposity but no change in overall body weight (68).

There are also intriguing clinically derived data concerning the effects of exercise on systemic inflammation. In noncancer patients, physical activity reduces levels of systemic inflammatory markers (69) and so exercise may enable modification of the negative proinflammatory effects of obesity. The anti-inflammatory effect of physical activity depends on exercise volume, intensity, and type, rather than on weight loss (70). Among prostate cancer patients, decreased CRP levels were found in prostate cancer patients following a 12-week program of resistance and aerobic exercise (71), and preliminary data from the Promenadgruppen study found significant changes in concentrations of adipokines and inflammatory markers compared with a control group in patients who underwent a 10-week small group walking program (unpublished data). Both study and control groups showed similar weight loss but the study group showed a 12 mm Hg reduction in systolic blood pressure, a 33% increase in levels of HDL, and a 60% reduction in CRP.

IL6 and TNFα are both raised in the serum of patients with metastatic carcinoma, compared with patients without metastases. Both are elevated in metastatic prostate cancer in direct proportion to disease stage, and increases occur at the time of biochemical disease progression (72). TNFα enhances the invasion of prostate cancer cell lines through synthesis of selectin ligands (73).

Adipokines

The serum levels of adipokines, produced by adipose tissue and playing roles in appetite, energy balance, and insulin resistance, vary depending on adiposity. Adipokines have potentially prooncogenic roles in angiogenesis and cell proliferation. Adiponectin has anti-inflammatory effects and its serum concentration is inversely correlated with adiposity. It dose-dependently reduces platelet aggregation (74) and suppresses inactivation of nitric oxide (NO, an inhibitor of platelet activation). Resistin is associated with insulin resistance through AMP kinase downregulation. It upregulates proinflammatory cytokines (IL6, TNFα) which act via the NF-κB pathway to increase proproliferative, proinflammatory, and antiapoptotic protein transcription. Nuclear

Published OnlineFirst July 7, 2016; DOI: 10.1158/1055-9965.EPI-16-0223

expression of NF-κb is associated with nodal metastasis in prostate cancer (75).

Immunologic impairment (NK cells)

NK-cell numbers in blood and in solid organs, together with their cytotoxicity and cytokine secretion, are reduced in obesity. Obese compared with nonobese patients have fewer circulating NK cells (76), and those with hypertension, raised fasting glucose, and unfavorable lipid profiles have less NK cells than "metabolically healthy" obese patients. Obese subjects have fewer hepatic NK cells and leptin receptor–positive cells compared with normal weight subjects (77). The NK-cell fraction of blood is sensitive to exercise (reviewed in ref. 78), and 5-fold increases in NK concentrations after exercise have been noted. Brief exercise upregulates molecular pathways in circulating NK cells associated with cancer and cell communication (79). In healthy young men, hypoxic exercise training leads to enhanced *in vitro* NK-cell cytotoxicity (80).

Obesity has substantial negative quantitative and qualitative effects on NK cells, the effector cells for killing circulating tumor cells (CTCs, see below). In addition, evidence suggests that interactions between platelets and CTCs can dramatically impair NK-cell–mediated immune editing.

Platelet cloaking of circulating tumor cells

Epithelial cells (having an $EpCAM^{+}$, $CD45^{-}$ immunophenotype) rarely exceed one cell per 7.5 mL of blood in patients without malignancy (81). CTC enumeration, using technologies such as the FDA-approved CellSearch system or the filtration-based ScreenCell system (ScreenCell) may have a prognostic role in advanced prostate cancer. A prospective study of castration-resistant prostate cancer found that $\geq$5 CTCs per 7.5 mL of blood correlated with a poor prognosis (82). When a variety of clinical, serologic, and pathologic parameters were considered, the model best predictive of survival was based on baseline LDH, baseline CTC count, and fold change in CTC count at monthly intervals (83).

Despite the long-recognized association between cancer and thromboembolism, it has been unclear whether the thrombocytosis often seen in patients with metastases is a consequence or cause of widespread tumor dissemination. Evidence now shows that platelets support tumor metastasis by various mechanisms (84). Platelets are involved in arrest of CTCs in the vasculature and through endothelial interactions enable their extravasation. Platelets also secrete various pro-oncogenic factors including PDGF and VEGF, and mediate prosurvival signals in ovarian cancer cells (85). Platelets can adhere to CTCs ("platelet cloaking") and may thereby impair NK-cell–mediated killing.

Tumor cell–induced platelet aggregation correlates with metastatic potential, and may be due to "cloaking" of tumor cells by adherent platelets. The interaction between CTC cloaking by platelets and their killing by NK cells is incompletely understood. Thrombocytopenic mice exhibited reduced tumor metastatic burden when tumor cells were NK-cell sensitive, and *in vitro* studies demonstrated reduced NK tumorilytic activity when platelets aggregated around tumor cells (ref. 86; Fig. 1). In a mouse model, deficiency for Gαq, a G-protein critical for platelet activation, markedly decreased experimental and spontaneous metastases (87). This effect was eliminated in NK-cell–deficient mice, further supporting the hypothesis that adherent platelets may obstruct the direct cell–cell contact required for NK-cell killing. Our group has recently demonstrated significant reductions in NK-cell activity (using flow cytometry for CD107a) through platelet cloaking of cancer cells, which appears to be mediated by the release of activated platelets (unpublished data). Release of TGFβ by adherent platelets, which downregulates the NK-cell–activating receptor NKG2D (88), may also inhibit NK-cell–tumor interactions. Platelets may enable evasion of NK-cell killing by conferring a "pseudonormal" phenotype on CTCs through high tumor cell surface expression of normal MHC class 1 antigen (89).

TF expression by tumor cells and the presence of serum factor XIII transglutaminase support metastasis by impeding NK-cell killing of CTCs (90, 91). Of note, prostasomes secreted by benign and malignant prostate cells contain high concentrations of TF, with strong procoagulant effects *in vitro* (92), suggesting a link between TF activity and platelet cloaking of CTCs.

In a murine model, platelets activated by CTC interactions release adenine nucleotides which, acting upon the endothelial P2Y2 receptor, open the endothelial barrier and facilitate transendothelial migration (93). An experimental antibody preferentially induces oxidative platelet fragmentation by targeting the β3 subunit of the platelet's fibrinogen receptor, reducing metastasis (94, 95). Platelet-derived TGFβ and direct platelet–tumor cell contacts activate TGFβ/Smad and NF-κB cancer cell pathways, resulting in EMT and enhanced metastasis in mice (96). All of these mechanisms require close interaction of tumor cells with platelets, interactions which can be described and quantified as platelet cloaking.

Demonstration that platelet cloaking is a mechanism by which obesity disimproves prostate cancer survival would suggest that therapies targeted at points along the pathway of platelet activation could be efficacious. For example, adiponectin supplementation or blockade of IL6 or TNFα could be useful. Comparison of the expression of lethality-associated genes between the primary site and CTCs could highlight genes which are upregulated as part of the metastatic pathway, with potential for targeted therapy.

The role of skeletal muscle

Skeletal muscle plays an important role in counteracting the proinflammatory effects of obesity. Contracting skeletal muscles release myokines which act as antagonists to the generally proinflammatory adipokines (reviewed in ref. 97). For example, although muscles produce IL6, a proinflammatory mediator which contributes to the deleterious effects of metabolic syndrome when chronically elevated, they do so in a TNFα-independent manner. Physically active people have low basal levels of IL6. High basal levels are associated with metabolic syndrome. This suggests a role for muscle-derived IL6 in metabolism rather than inflammation, and IL6 stimulates insulin-mediated glucose uptake in muscle cells *in vitro*. Other myokines include IL15, which decreases lipid deposition in preadipocytes, and myostatin, whose expression is reduced by aerobic and strength exercise. The overall effects of the skeletal muscle secretome involve muscle hypertrophy, adipose tissue oxidation, increasing insulin sensitivity, increasing osteogenesis, reducing inflammation, increasing antitumor activity, and increasing pancreatic function. Obese men are characterized by sarcopenic obesity, and their reduced muscle mass contributes

Published OnlineFirst July 7, 2016; DOI: 10.1158/1055-9965.EPI-16-0223

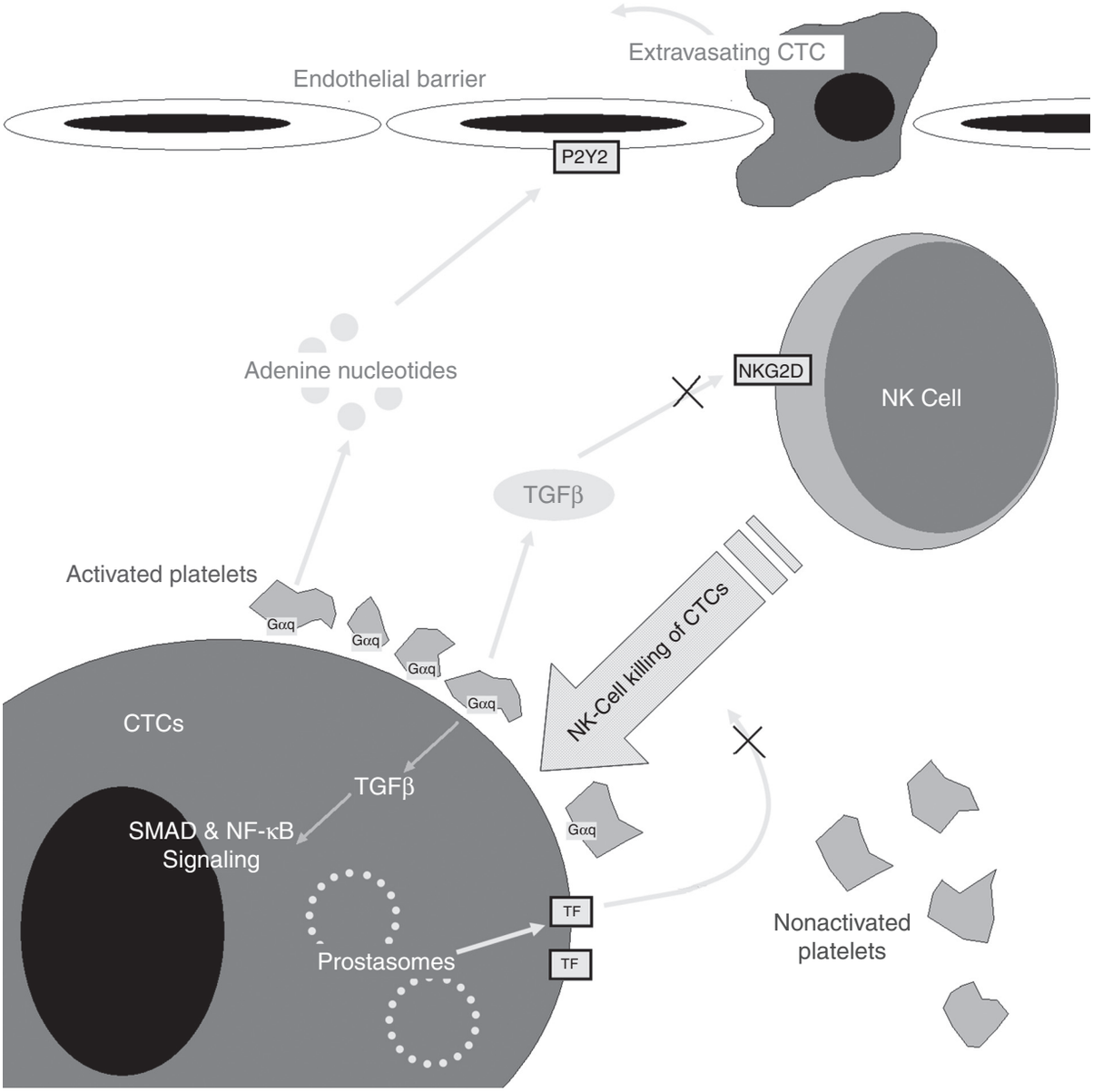

Figure 1.

Activated platelets, expressing Gαq, adhere to prostate cancer CTCs and release TGFβ, impairing NK-cell activation through NKG2D downregulation. CTC-expressed tissue factor also impairs NK-cell killing, probably by direct obstruction by the platelet cloak. Adenine nucleotides from activated platelets open the endothelial barrier via endothelial P2Y2, and epithelial–mesenchymal transition and invasiveness is promoted by platelet-derived TGFβ-mediated activation of NF-κB and SMAD pathways within CTCs.

substantially to insulin resistance and metabolic syndrome. Skeletal muscle–derived factors interact substantially with those derived from adipose tissue, and increasing skeletal muscle mass as well as reducing adiposity is likely to be of benefit in reducing platelet cloaking of CTCs. The sarcopenia caused by ADT may be responsive to antagonists of myostatin (98). Myostatin negatively regulates skeletal muscle growth and is a member of the TGFβ superfamily. Chronic myostatin exposure can cause apoptosis in cancer cells, through a shift from oxidative phosphorylation to glycolysis (99).

Conclusions

Because of the combination of an aging population and rising levels of obesity, a "perfect storm" of increased incidence and aggressiveness of prostate cancer is imminent. Low-cost interventions are required which can improve QoL and modify disease biology independent of the various surgical, radiologic, and pharmacologic options already available. Although the mechanisms by which it does so are incompletely understood, the proinflammatory and prothrombotic milieu associated with obesity appears to

Published OnlineFirst July 7, 2016; DOI: 10.1158/1055-9965.EPI-16-0223

be the pathway through which this lifestyle-modifiable disease exerts its aggressive effects in prostate cancer. There is increasing observational and experimental evidence that exercise can modify the biology of prostate cancer and ameliorate some of the deleterious effects of obesity in these patients. Further focused research is required both to prove the disease-modifying effects of exercise and to explore the useful underlying mechanisms.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

This work was supported by World Cancer Research Fund, grant number 2013/1003 (£250,000; to S.P. Finn).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received March 11, 2016; revised June 3, 2016; accepted June 27, 2016; published OnlineFirst July 7, 2016.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69–90..
2. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. J Cancer Surviv 2010;4:87–100.
3. Voskuil DW, Monninkhof EM, Elias SG, Vlems FA, van Leeuwen FE; Task force physical activity and cancer. Physical activity and endometrial cancer risk, a systematic review of current evidence. Cancer Epidemiol Biomarkers Prev 2007;16:639–48.
4. Boyle T, Keegel T, Bull F, Heyworth J, Fritschi L. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. J Natl Cancer Inst 2012;104:1548–61.
5. Keimling M, Behrens G, Schmid D, Jochem C, Leitzmann MF. The association between physical activity and bladder cancer: a systematic review and meta-analysis. Br J Cancer 2014;110:1862–70.
6. Behrens G, Leitzmann MF. The association between physical activity and renal cancer: systematic review and meta-analysis. Br J Cancer 2013;108:798–811.
7. Behrens G, Jochem C, Keimling M, Ricci C, Schmid D, Leitzmann MF. The association between physical activity and gastrooesophageal cancer: systematic review and meta-analysis. Eur J Epidemiol 2014;29:151–70.
8. Wu Y, Zhang D, Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. Breast Cancer Res Treat 2013;137:869–82.
9. Jochem C, Leitzmann MF, Keimling M, Schmid D, Behrens G. Physical activity in relation to risk of hematologic cancers: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014;23:833–46.
10. Ligibel JA, Campbell N, Partridge A, Chen WY, Salinardi T, Chen H, et al. Impact of a mixed strength and endurance exercise intervention on insulin levels in breast cancer survivors. J Clin Oncol 2008;26:907–12.
11. Tomlinson D, Diorio C, Beyene J, Sung L. Effects of exercise on cancer-related fatigue: a meta-analysis. Am J Phys Med Rehabil 2014;93:675–86.
12. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev 2012;11:CD006145.
13. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. Cochrane Database of Syst Rev 2012;8:CD008465.
14. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddigi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer surivivors: a systematic review. J Natl Cancer Inst 2012;104:815–40.
15. Irwin ML, McTiernan A, Manson JE, Thomson CA, Sternfeld B, Stefanick ML, et al. Physical activity and survival in postmenopausal women with breast cancer: results from the women's health initiative. Cancer Prev Res 2011;4:522–9.
16. West-Wright CN, Henderson KD, Sullivan-Halley J, Ursin G, Deapen D, Neuhausen S, et al. Long-term and recent recreational physical activity and survival after breast cancer: the California Teachers Study. Cancer Epidemiol Biomarkers Prev 2009;18:2851–9.
17. Haydon AMM, MacInnis RJ, English DR, Giles GG. Effect of physical activity and body size on survival after diagnosis with colorectal cancer. Gut 2006;55:62–7.
18. Meyerhardt JA, Giovannucci EL, Ogino S, Kirkner GJ, Chan AT, Willett W, et al. Physical activity and male colorectal cancer survival. Arch Intern Med 2009;169:2102–8.
19. Meyerhardt JA, Giovannucci EL, Holmes MD, Chan AT, Chan JA, Colditz GA, et al. Physical activity and survival after colorectal cancer diagnosis. J Clin Oncol 2006;24:3527–34.
20. Courneya KS, Friedenreich CM, Franco-Villalobos C, Crawford JJ, Chua N, Basi S, et al. Effects of supervised exercise on progression-free survival in lymphoma patients: an exploratory follow-up of the HELP trial. Cancer Causes Control 2015;26:269–76.
21. Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the Health Professionals Follow-Up Study. Int J Cancer 2007;121:1571–8.
22. Friedenreich CM, McGregor SE, Courneya KS, Angyalfi SJ, Elliott FG. Case-Control study of lifetime total physical activity and prostate cancer risk. Am J Epidemiol 2004;159:740–9.
23. Johnsen NF, Tjønneland A, Thomsen BL, Christensen J, Loft S, Friedenreich C, et al. Physical activity and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Int J Cancer 2009;125:902–8.
24. Giovannucci EL, Liu Y, Leitzmann MF, Stampfer MJ, Willett WC. A prospective study of physical activity and incident and fatal prostate cancer. Arch Intern Med 2005;165:1005–10.
25. Patel AV, Rodriguez C, Jacobs EJ, Solomon L, Thun MJ, Calle EE. Recreational physical activity and risk of prostate cancer in a large cohort of U.S. men. Cancer Epidemiol Biomarkers Prev 2005;14:275.
26. Littman AJ, Kristal AR, White E. Recreational physical activity and prostate cancer risk (United States). Cancer Causes Control 2006;17:831–41.
27. Nilsen TI, Romundstad PR, Vatten LJ. Recreational physical activity and risk of prostate cancer: A prospective population-based study in Norway (the HUNT study). Int J Cancer 2006;119:2943–7.
28. Wiklund F, Lageros YT, Chang E, Bälter K, Johansson JE, Adami HO, et al. Lifetime total physical activity and prostate cancer risk: a population-based case-control study in Sweden. Eur J Epidemiol 2008;23:739–46.
29. Zeegers MA, Dirx MJM, Van Den Brandt PA. Physical activity and the risk of prostate cancer in the Netherlands Cohort Study, results after 9.3 years of follow-up. Cancer Epidemiol Biomarkers Prev 2005;14:1490–5.
30. Keogh JWL, MacLeod RD. Body composition, physical fitness, functional performance, quality of life, and fatigue benefits of exercise for prostate cancer patients: a systematic review. J Pain Symptom Manage 2012;43:96–110.
31. Gardner JR, Livingston PM, Fraser SF. Effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy: a systematic review. J Clin Oncol 2014;32:335–46.
32. Kapur G, Windsor PM, McCowan C. The effect of aerobic exercise on treatment-related acute toxicity in men receiving radical external beam radiotherapy for localized prostate cancer. Eur J Cancer Care (Engl) 2010;19:643–7.
33. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, et al. Randomised controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. J Clin Oncol 2009;27:344–51.
34. Culos-Reed SN, Robinson JW, Lau H, Stephenson L, Keats M, Norris S, et al. Physical activity for men receiving androgen deprivation therapy for

prostate cancer: benfits from a 16-week intervention. Support Care Cancer 2010;18:591–9.
35. Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM. Physical activity and survival after prostate cancer diagnosis in the Health Professionals Follow-Up Study. J Clin Oncol 2011;29:726–32.
36. Richman EL, Kenfield SA, Stampfer MJ, Paciorek A, Carroll PR, Chan JM. Physical activity after diagnosis and risk of prostate cancer progression: data from the Cancer of the prostate strategic urologic research endeavor. Cancer Res 2011;71:3889–95.
37. Bonn SE, Sjolander A, Lagerros YT, Wiklund F, Stattin P, Holmberg E, et al. Physical activity and survival among men diagnosed with prostate cancer. Cancer Epidemiol Biomarkers Prev 2015;24:57–64.
38. Friedenreich CM, Wang Q, Neilson HK, Kopciuk KA, McGregor SE, Courneya KS. Physical activity and survival after prostate cancer. Eur Urol 2016 Jan 7. [Epub ahead of print].
39. Sellar CM, Bell GJ, Haennel RG, Au HJ, Chua N, Courneya KS. Feasibility and efficacy of a 12-week supervised exercise intervention for colorectal cancer survivors. Appl Physiol Nutr Metab 2014;39:715–23.
40. Peddle-McIntyre CJ, Bell G, Fenton D, McCargar L, Courneya KS. Feasibility and preliminary efficacy of progressive resistance exercise training in lung cancer survivors. Lung Cancer 2012;75:126–32.
41. Broderick J, Guinan E, Kennedy MJ, Hollywood D, Courneya KS, Culos-Reed N, et al. Feasibility and efficacy of a supervised exercise intervention in de-conditioned cancer survivors during the early survivorship phase: the PEACH trial. J Cancer Surviv 2013;7:551–62.
42. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. JAMA 2014;311:806–14.
43. Smith JC, Bennett S, Evans LM, Kynaston HG, Parmar M, Mason MD, et al. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. J Clin Endocrinol Metab 2001;86:4261–7.
44. Dockery F, Bulpitt CJ, Agarwal S, Donaldson M, Rajkumar C. Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. Clin Sci 2003;104:195–201.
45. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab 2006;91:1305–8.
46. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst 2010;102:39–46.
47. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448–56.
48. Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol 2006;24:3979–83.
49. Van Hemelrijck M, Garmo H, Holmberg L, Ingelsson E, Bratt O, Bill-Axelson A, et al. Absolute and relative risk of cardiovascular disease in men with prostate cancer: results from the population-based PCBaSe Sweden. J Clin Oncol 2010;28:3448–56.
50. Smith MR, Bae K, Efstathiou JA, Hanks GE, Pilepich MV, Sandler HM, et al. Diabetes and mortality in men with locally advanced prostate cancer: RTOG 92–02. J Clin Oncol 2008;26:4333–9.
51. Ma J, Li H, Giovannucci E, Mucci L, Qiu W, Nguyen PL, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. Lancet Oncol 2008;9:1039–47.
52. Laukkanen JA, Laaksonen DE, Niskanen L, Pukkala E, Hakkarainen A, Salonen JT. Metabolic syndrome and the risk of prostate cancer in Finnish men: a population-based study. Cancer Epidemiol Biomarkers Prev 2004;13:1646–50.
53. Tande AJ, Platz EA, Folsom AR. The metabolic syndrome is associated with reduced risk of prostate cancer. Am J Epidemiol 2006;164:1094–102.
54. Aggarwal RR, Ryan CJ, Chan JM. Insulin-like growth factor pathway: a link between androgen deprivation therapy (ADT), insulin resistance, and disease progression in patients with prostate cancer? Urol Oncol 2013;31:522–30.
55. Luo J, Murphy LJ. Differential expression of the insulin-like growth factor binding proteins in spontaneously diabetic rats. J Mol Endocrinol 1992;8:155–63.
56. Hellawell GO, Turner GD, Davies DR, Poulsom R, Brewster SF, Macaulay VM. Expression of the type 1 insulin-like growth factor receptor is up-regulated in primary prostate cancer and commonly persists in metastatic disease. Cancer Res 2002;62:2942–50.
57. Ryan CJ, Hagg CM, Simko J, Nonaka DF, Chan JM, Weinberg V, et al. Expression of insulin-like growth factor-1 receptor in local and metastatic prostate cancer. Urol Oncol 2007;25:134–40.
58. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract 2014;105:141–50.
59. Zhang N, Lawrence DA. Tissue factor and obesity, a two-way street. Nat Med 2011;17:1343–4.
60. Badeanlou L, Furlan-Freguia C, Yang G, Ruf W, Samad F. Tissue factor-protease-activated receptor 2 signaling promotes diet-induced obesity and adipose inflammation. Nat Med 2011;17:1490–8.
61. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-α: direct role in obesity-linked insulin resistance. Science 1993;259:87–91.
62. Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome. A comprehensive perspective based on interactions between obesity, diabetes, and inflammation. Circulation 2005;111:1448–54.
63. Rundqvist H, Augsten M, Stromberg A, Rullman E, Mijwel S, Kharaziha P, et al. Effect of acute exercise on prostate cancer cell growth. PLoS ONE 2013;8:e67579.
64. Soliman S, Aronson WJ, Barnard RJ. Analyzing serum-stimulated prostate cancer cell lines after low-fat, high-fibre diet and exercise intervention. Evid Based Complement Alternat Med 2011;2011:529053.
65. Leung PS, Aronson WJ, Ngo TH, Golding LA, Barnard RJ. Exercise alters the IGF axis *in vivo* and increases p53 protein in prostate tumour cells *in vitro*. J Appl Physiol 2004;96:450–4.
66. Ornish D, Weidner G, Fair WR, Marlin R, Pettengill EB, Raisin CJ, et al. Intensive lifestyle changes may affect the progression of prostate cancer. J Urol 2005;174:1065–70.
67. Jones LW, Antonelli J, Masko EM, Broadwater G, Lascola CD, Fels D, et al. Exercise modulation of the host-tumor interaction in an orthotopic model of murine prostate cancer. J Appl Physiol 2012;113:263–72.
68. Zheng X, Cui XX, Huang MT, Liu Y, Shih WJ, Lin Y, et al. Inhibitory effect of voluntary running wheel exercise on the growth of human pancreas Panc-1 and prostate PC-3 xenograft tumors in immunodeficient mice. Oncol Rep. 2008;19:1583–8.
69. Ho SS, Dhaliwal SS, Hills AP, Pal S. Effects of chronic exercise training on inflammatory markers in Australian overweight and obese individuals in a randomized controlled trial. Inflammation 2012 Dec 19. [Epub ahead of print].
70. Balducci S, Zanuso S, Nicolucci A, Fernando F, Cavallo S, Cardelli P, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. Nutr Metab Cardiovasc Dis 2010;20:608–17.
71. Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomised controlled trial. J Clin Oncol 2010;28:340–7.
72. Michalaki V, Syrigos K, Charles P, Waxman J. Serum levels of IL-6 and TNFα correlate with clinicopathological features and patient survival in patients with prostate cancer. Br J Cancer 2004;90:2312–6.
73. Radhakrishnan P, Chachadi V, Lin MF, Singh R, Kannagi R, Cheng PW. TNFα enhances the motility and invasiveness of prostatic cancer cells by stimulating the expression of selective glycosyl- and sulfotransferase genes involved in the synthesis of selectin ligands. Biochem Biophys Res Comm 2011;409:436–41.
74. Restituto P, Colina I, Varo JJ, Varo N. Adiponectin diminishes platelet aggregation and sCD40L release. Potential role in the metabolic syndrome. Am J Physiol Endocrinol Metab 2010;298:E1072–7.
75. Ismail HA, Lessard L, Mes-Masson AM, Saad F. Expression of NF-kappaB in prostate cancer lymph node metastases. Prostate 2004;58:308–13.
76. Lynch LA, O'Connell JM, Kwasnik AK, Cawood TJ, O'Farrelly C, O'Shea DB. Are natural killer cells protecting the metabolically healthy obese patient? Obesity 2009;17:601–5.

Published OnlineFirst July 7, 2016; DOI: 10.1158/1055-9965.EPI-16-0223

77. Lautenbach A, Breitmeier D, Kuhlmann S, Nave H. Human obesity reduces the number of hepatic leptin receptor (Ob-R) expressing NK-cells. Endocr Res 2011;36:158–66.
78. Timmons BW, Cieslak T. Human natural killer cell subsets and acute exercise: a brief review. Exerc Immunol Rev 2008;14:8–23.
79. Radom-Azik S, Zaldivar FP, Haddad F, Cooper DM. Impact of brief exercise on peripheral blood NK-cell gene and microRNA expression in young adults. J Appl Physiol. 2013 Jan 3. [Epub ahead of print].
80. Wang JS, Weng TP. Hypoxic exercise training promotes antitumour cytotoxicity of natural killer cells in young men. Clin Sci 2011;121:343–53.
81. Allard WJ, Matera J, Miller MC, Repollet M, Connelly MC, Rao C, et al. Tumor cells circulate in the peripheral blood of all major carcinomas but not in healthy subjects or patients with nonmalignant diseases. Clin Cancer Res 2004;10:6897–904.
82. De Bono, Scher HI, Montgomery RB, Parker C, Miller MC, Tissing H, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. Clin Cancer Res 2008;14:6302–9.
83. Scher HI, Jia X, de Bono JS, Fleisher M, Pienta KJ, Raghavan D, et al. Circulating tumour cells as prognostic markers in progressive, castration-resistant prostate cancer: a reanalysis of IMMC38 trial data. Lancet Oncol 2009;10:233–9.
84. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer 2011;11:123–34.
85. Egan K, Crowley D, Smyth P, O'Toole S, Spillane C, Martin C, et al. Platelet adhesion and degranulation induce pro-survival and pro-angiogenic signaling in ovarian cancer cells. PLoS One 2011;6:e26125.
86. Nieswandt B, Hafner M, Echtenacher B, Männel DN. Lysis of tumor cells by natural killer cells in mice is impeded by platelets. Cancer Res 1999;59:1295–300.
87. Palumbo JS, Talmage KE, Massari JV, La Jeunesse CM, Flick MJ, Kombrinck KW, et al. Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. Blood 2005;105:178–85.
88. Kopp HG, Placke T, Salih HR. Platelet-derived transforming growth factor-β down-regulates NKG2D thereby inhibiting natural killer cell antitumor reactivity. Cancer Res 2009;69:7775–83.
89. Placke T, Orgel M, Schaller M, Jung G, Rammensee HG, Kopp HG, et al. Platelet-derived MHC class I confers a pseudonormal phenotype to cancer cells that subverts the antitumour reactivity of natural killer immune cells. Cancer Res 2012;72:440–48.
90. Palumbo JS, Talmage KE, Massari JV, La Jeunesse CM, Flick MJ, Kombrinck KW, et al. Tumor cell-associated tissue factor and circulating hemostatic factors cooperate to increase metastatic potential through natural killer cell-dependent and –independent mechanisms. Blood 2007;110:133–41.
91. Palumbo JS, Barney KA, Blevins EA, Shaw MA, Mishra A, Flick MJ, et al. Factor XIII transglutaminase supports haematogenous tumor cell metastasis through a mechanism dependent on natural killer cell function. J Thromb Haemost 2008;6:812–9.
92. Babiker AA, Hamad OA, Sanchez J, Ronquist G, Nilsson B, Nilsson Ekdahl K. Prothrombotic effect of prostasomes of metastatic cell and seminal origin. Prostate 2007;67:378–88.
93. Schumacher D, Strilic B, Sivaraj KK, Wettschureck N, Offermanns S. Platelet-derived nucleotides promote tumor-cell transendothelial migration and metastasis via P2Y2 receptor. Cancer Cell 2013;24:130–7.
94. Zhang W, Dang S, Hong T, Tang J, Fan J, Bu D, et al. A humanized single-chain antibody against beta 3 integrin inhibits pulmonary metastasis by preferentially fragmenting activated platelets in the tumor microenvironment. Blood 2012;120:2889–98.
95. Ware J. Fragmenting the platelet to reduce metastasis. Blood 2012;120:2779–80.
96. Labelle M, Begum S, Hynes RO. Direct signalling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Cancer Cell 2011;20:576–90.
97. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol 2012;8:457–65.
98. Padhi D, Higano CS, Shore ND, Sieber P, Rasmussen E, Smith MR. Pharmacological inhibition of myostatin and changes in lean body mass and lower extremity muscle size in patients receiving androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab 2014;99:E1967–75.
99. Liu Y, Cheng H, Zhou Y, Zhu Y, Bian R, Chen Y, et al. Myostatin induces mitochondrial metabolic alteration and typical apoptosis in cancer cells. Cell Death Dis 2013;4:e494

Published OnlineFirst July 7, 2016; DOI: 10.1158/1055-9965.EPI-16-0223

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Exercise and Prostate Cancer: Evidence and Proposed Mechanisms for Disease Modification

Brian D. Hayes, Lauren Brady, Michael Pollak, et al.

Cancer Epidemiol Biomarkers Prev 2016;25:1281-1288. Published OnlineFirst July 7, 2016.