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State of the epidemiological evidence on physical activity and cancer prevention

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ABSTRACT

Background: Physical activity is a modifiable lifestyle risk factor that has the potential to reduce the risk of most major cancer sites.

Methods: We examined the strength, consistency, dose–response and biological plausibility of an association between physical activity and risk of colon, breast, endometrium, lung, prostate, ovarian, gastric, rectal, pancreatic, bladder, testicular, kidney and haematological cancers. We also estimated the population-attributable risk (PAR) for physical inactivity and cancer in 15 European countries.

Results: There is convincing or probable evidence for a beneficial effect of physical activity on the risk of colon, breast and endometrial cancers. The evidence is weaker for ovarian, lung and prostate cancers and generally either null or insufficient for all remaining cancers. Several hypothesised biological mechanisms include a likely effect of physical activity on insulin resistance, body composition, sex steroid hormones and a possible effect on vitamin D, adipokines, inflammation and immune function. Somewhere between 165,000 and 330,000 cases of the six major cancers (breast, colon, lung, prostate, endometrium and ovarian) could have been prevented in 2008 in Europe alone if the population had maintained sufficient levels of physical activity.

Conclusion: There is strong and consistent evidence that physical activity reduces the risk of several of the major cancer sites, and that between 9% and 19% of cancer cases could be attributed to lack of sufficient physical activity in Europe. Public health recommendations for physical activity and cancer prevention generally suggest 30–60 min of moderate or vigorous-intensity activity done at least 5 d per week.

1. Introduction

The past 20 years of epidemiological research has generated a large body of evidence describing the benefits of physical activity in relation to cancer risk. Despite great progress in understanding this association, particularly with respect to colon and breast cancers, there is still uncertainty regarding the strength, consistency and dose–response of the associations between physical activity and most other cancer sites. It is also unclear what type, timing and dose of activity are required for significant benefit and also the population subgroups that experience a reduced cancer risk with physical activity. To address the state of the knowledge surrounding these questions, we will provide an overview of the existing epidemiological evidence relating physical activity to cancer risk. Using the latest published literature, we also estimate

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the proportion of cancers that are attributable to inadequate physical activity levels in Europe and describe briefly some proposed biological mechanisms explaining physical activity–cancer relations. We finally highlight areas for future research.

2. Epidemiological evidence for an association between physical activity and cancer

The association between physical activity and all cancer sites has been systematically reviewed by national[1] and international agencies[2,3] as well as by individual scientists.[4,5] The level of epidemiological evidence varies by cancer site. There is now convincing evidence for a beneficial effect of physical activity on the risk of colon cancer, probable evidence for an effect on breast and endometrial cancers, possible evidence for an effect on cancers of the prostate, lung and ovary, and insufficient or null evidence for most remaining cancer sites. In the sections below, we describe the strength, consistency and dose–response for these associations, as well as any evidence for an effect within population sub-groups.

2.1. *Cancers convincingly or probably associated with physical activity*

2.1.1. *Colon cancer*

Colon cancer has received much research attention relative to other cancer sites with respect to the aetiological role of physical activity. Over 60 studies have been conducted worldwide on the association between physical activity and colon or colorectal cancers.[2,3,6–8] These studies have used diverse populations and settings and assessed different types, parameters and time periods when physical activity was performed and considered some of the effect modifiers that may influence this association. These reviews have estimated that physical activity reduces colon cancer risk by 20–25% amongst both men and women who undertake the highest level of assessed physical activity compared with the lowest level of activity.[1,5,6,8,9] A somewhat stronger risk reduction is observed in case–control than in cohort studies (24% versus 17%).[6] Occupational activity reduces risk to the same extent as recreational activity (22% versus 23%). Evidence for a dose–response effect exists with greater risk reductions observed for higher levels of activity.[6,8] Although formal meta-analyses of the different effects of intensity and duration have not been performed because of the lack of detail on these parameters reported in previous studies, one qualitative assessment has suggested that vigorous-intensity activity is needed to reduce colon cancer risk[10] whilst another has suggested that moderate-intensity activity may be sufficient.[5] Based on the overall evidence from studies of recreational activity, about 30–60 min per day of moderate to vigorous-intensity physical activity may be needed to lower colon cancer risk significantly.[11]

The association between physical activity and colon cancer risk may vary across population sub-groups. Risk benefit remains relatively constant across different strata of the body mass index (BMI weight/height^2).[6] It is less clear whether or not the benefits of physical activity depend on menopausal hormone therapy use, race/ethnicity, dietary intake or tumour sub-site. Some studies have observed a greater effect of physical activity on the proximal colon[12–16] and others on the distal colon.[17,18] These differences in effects by tumour sub-site may have implications for colon cancer screening by colonoscopy that is most effective for distal tumours.

2.1.2. *Breast cancer*

Extensive research has been conducted on the aetiological role of physical activity in relation to breast cancer risk with 73 separate studies published to date. More than three quarters of these studies have observed a beneficial effect of physical activity on breast cancer risk. The risk reduction, for those studies that found this benefit, is about 25% when comparing the most to least active study participants.[1,19,20] There is also consistent evidence of a dose–response effect of decreasing risk with increasing activity levels observed in the majority of studies that examined the trend. The effect of physical activity is somewhat more evident in case–control than cohort studies with average risk reductions of 30% versus 20%, respectively. All types of activity are beneficial for breast cancer risk reduction with somewhat stronger effects observed for recreational and household activity (average 21%) followed by walking/cycling (18%) and occupational activity (13%).[19] Physical activity reduces breast cancer risk when performed at any age throughout life, but activity done after the age of 50 years does have a stronger effect on risk than activity done earlier in life and sustained lifetime activity is of benefit.[19]

When considering the effect of physical activity within population sub-groups, a greater benefit of physical activity is observed for postmenopausal women, women with a normal BMI, parous women, non-Caucasian women and women without a family history of breast cancer.[19] No clear pattern of effect modification by hormone receptor status is yet discernible. More evidence for an effect of physical activity on ER+ or PR+ tumours exists than for ER– or PR– tumours when these receptors are examined separately. However, when the combined hormone receptor status is considered, few statistically significant risk reductions exist, with some evidence for greater risk reductions in women with ER–/PR– tumours (27%) than for women with ER+/PR+ tumours (14%).[19]

While a few aspects of this association remain unclear, including whether or not the benefit of physical activity depends on the histological type of the tumour, the hormone receptor status and the effect modification by other biological mechanisms involved in breast cancer aetiology, there is already sufficient evidence to recommend physical activity as a means of reducing breast cancer risk. Current public health recommendations for breast cancer risk reduction are for at least 4–7 h per week of moderate to vigorous-intensity activity.[1]

2.1.3. *Endometrial cancer*

Epidemiological evidence now exists that physical activity probably protects against endometrial cancer and that this effect is independent of adiposity.[3,21,22] A recent systematic review by Voskuil and colleagues[22] of 20 studies found a consistent reduction in endometrial cancer risk with a range in risk reduction of about 20–30% depending on the study

design and quality. Another review by Cust and colleagues[21] concluded that there was convincing or probable evidence that physical activity reduces endometrial cancer risk in the majority of the studies included, with an average risk reduction of 30%. There was evidence for a dose–response effect in about half of the studies. While all types of activity appear to decrease endometrial cancer risk to the same extent, there is some evidence for a beneficial effect associated with household activities and walking or cycling done as transportation to work. Of interest is that sedentary behaviour is emerging as a risk factor for endometrial cancer in a few studies that have examined risk associated with sitting for more than 5 h daily.[23–25] There is also some evidence that higher intensity and longer duration activities confer a somewhat greater decrease in risk than lower intensity, shorter duration activities. The evidence regarding the benefit of physical activity done in different age periods in life is more limited with some studies observing a stronger effect with recent or lifetime activity than activity done earlier in life. There is no consistent evidence regarding the effect of physical activity on endometrial cancer risk for different population sub-groups including different BMI categories, menopausal status and other risk factors.

Based on the studies conducted to date, about 1 h daily of moderate-intensity activity appears to confer a benefit for endometrial cancer risk.[21,22] Further research that includes more detailed assessments of lifetime physical activity, which considers all types and parameters of activity done throughout a lifetime, is needed, as well as more comprehensive examination of the effects within population sub-groups.[21,22]

2.2. *Cancers possibly associated with physical activity*

2.2.1. *Lung cancer*

Over 20 separate studies have been conducted on physical activity and lung cancer risk with most, but not all, demonstrating a risk reduction ranging from 20% to 40%. Stronger risk decreases were observed in studies that did not fully control for smoking, a strong confounder of this relation.[2,3,5,26,27] The inconsistencies in previous studies may be attributable to a number of factors including small sample sizes, residual confounding by smoking or imprecise and incomplete assessment of physical activity. Since the aetiology of lung cancer may differ by smoking status,[28,29] controlling for the effect of smoking or examining the risk amongst non-smokers has emerged as an important methodological consideration for this cancer site. There is either no effect or a diminished effect of physical activity on lung cancer risk amongst non-smokers in the studies that stratified their results by smoking status.[27] Hence, the substantial risk reductions demonstrated in some studies reflect the protective effect physical activity confers for smokers only, an important consideration when interpreting the estimated number of preventable lung cancer cases. The effect appears to be stronger for recreational than occupational activity, and stronger in men than in women, but consistent across different histological subtypes. Insufficient studies have examined the effect of physical activity by age, ethnic or racial groups, BMI or other possible effect modifiers to make any conclusions regarding the nature of the association in those population sub-groups.[2,3,5,26,27]

2.2.2. *Prostate cancer*

There is inconsistent evidence regarding the association between physical activity and prostate cancer, with about one-third of the studies conducted thus far indicating a protective effect of activity on risk.[1,30,31] The magnitude of the risk reduction is modest, ranging from 10% to 20%, and there remains a lack of clarity on the questions of what type, parameters and time periods in life are most beneficial for prostate cancer risk reduction. Furthermore, it is unknown if the benefit from physical activity varies according to other factors such as age, race, family history or BMI. Some evidence exists that the effect of physical activity may be greater in advanced prostate cancers[1–3,5] and for higher levels of lifetime physical activity.[32,33]

Some methodological issues pertinent to prostate cancer and physical activity studies need to be considered when reviewing these findings. Selection bias may occur because healthier, physically active men may be more likely to be screened for prostate cancer, and hence more likely to be diagnosed, than less active men. Consequently, some study populations might not have accurately reflected the general population of cancer patients. Second, since prostate cancer is a slow-growing tumour with a long latency period, a large percentage of men will die with evidence of undiagnosed prostate cancer. Therefore, it may have been difficult to detect a difference in physical activity levels between the cancer cases and the 'healthy' control populations because of latent, non-clinical prostate cancer amongst the controls rendering the two populations too similar.

2.2.3. *Ovarian cancer*

More than 20 studies have been conducted on the role of physical activity in ovarian cancer aetiology, with inconsistent findings: half of them observed a benefit, half of them found no effect and one study reported an increased risk.[2,3,34] In addition, evidence for a dose–response trend was not consistently observed for all types of activity. A recent meta-analysis of six case–control and six cohort studies conducted by Olsen et al.[34] estimated about a 20% risk reduction between recreational physical activity and ovarian cancer. The effect appears to be somewhat stronger for recreational activity than occupational activity.[34] Sedentary behaviour has been identified as a risk factor for ovarian cancer in two studies[35,36] with up to a 55% increase in risk for six or more hours per day of sitting. Results surrounding the intensity of physical activity have been very disparate with several studies reporting *increased* risks for vigorous-intensity activity,[37–39] while others have observed decreased risks for strenuous activities[40–43] or no difference between moderate and vigorous-intensity activities and ovarian cancer risk.[34,44,45] There does not appear to be a particular age or life period in which physical activity exerts a greater benefit on ovarian cancer risk, with studies generally finding a consistent effect across all ages.[34] Likewise, no effect modification by BMI, menopausal status, hormone use, smoking habits, parity, family history or histological sub-type has been found thus far. However, most of these studies were not large enough to permit adequate sub-group analyses to be conducted. Thus, although more than 20 studies have been published on the association between physical activity and ovarian cancer, uncertainty

remains about the association because of the inconsistency of the results.

2.3. Null or insufficient associations with physical activity

For the remaining cancer sites not mentioned above, the associations between physical activity and cancer are either null or classified as insufficient because of the lack of published research.

For the haematological cancers there have been between one and eight studies conducted for each of non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma, leukaemia and multiple myeloma.[5] These studies have been limited by small sample sizes, crude physical activity assessments, lack of control for confounding or consideration of effect modification. Overall, there is some suggestion of a protective effect of recreational physical activity for NHL and leukaemia, but no evidence exists for such a beneficial effect for multiple myeloma or Hodgkin's lymphoma.

For cervical cancer, only four studies have been published that were specifically designed to assess the association between physical activity and cervical cancer risk.[46–49] The results have been inconsistent, with slightly increased and decreased risks observed. These studies were also hampered by the lack of control for human papilloma virus exposure and sexual behaviour.

In contrast with the evidence for colon and colorectal cancer, there is convincing evidence for a lack of association between physical activity and rectal cancer.[1,8] Three meta-analyses have been conducted that have all concluded that there is no association.[3,7,50]

For gastric cancer, only four cohort studies[49,51–53] have found a decreased risk associated with increased physical activity levels in the over 15 studies conducted to date. One methodological issue for this cancer is possible effect modification by histological sub-type, which has not been examined in most of the previous studies. This point is of particular relevance for oesophageal cancer, for which the association has been found to vary according to anatomical location of the tumour, as well as histological sub-type.[53] Only five studies have been conducted on oesophageal cancer and physical activity[54] with limited evidence for an effect observed thus far. This is despite the potential biological mechanism that exists given the strong association of obesity with oesophageal adenocarcinoma, and the potential role that physical activity could have in reducing obesity as a risk factor.

At least 13 studies have examined relations between physical activity and pancreatic cancer.[30] Overall, there is insufficient evidence that physical activity reduces pancreatic cancer risk, as the results have been mainly null, although benefits have been suggested in a few studies.[1] A weak, positive association exists between BMI and pancreatic cancer, which could hypothetically be mitigated by physical activity.

For the remaining genitourinary cancers including kidney, testicular and bladder, there is insufficient evidence regarding the effect of physical activity.[2,5] For kidney cancer, an equal number of studies have found no effect or a beneficial effect of activity on risk.[30] For testicular cancer there has been some suggestion of an increased risk associated with cycling and horseback riding; however, this suggested association was not corroborated in the most recent case–control study on this topic.[55] Furthermore, a decreased risk with specific histological sub-types of testicular cancer was also recently found to be associated with childhood physical activity.[56] For bladder cancer, the majority of studies to date have found no association between physical activity and risk and a couple have even suggested a possible increased risk, but those studies had some methodological limitations (e.g. small number of cases) that hinder their interpretation.[57]

3. Population-attributable risks in Europe

From a public health perspective, a need exists to examine the burden of cancer that might be preventable if risks associated with a specific lifestyle factor could be removed or, at least minimised in a population. To estimate the cancer burden in Europe attributable to physical inactivity, we used physical activity estimates generated by Eurobarometer, Wave 58.2 conducted in 15 European Union countries in 2002[58] and estimates of gender-specific cancer incidence in 2008 reported by Ferlay and colleagues.[59] Eurobarometers are population-level public opinion surveys conducted for the European Commission. Eurobarometer, Wave 58.2, used the short-form International Physical Activity Questionnaire (IPAQ) to assess physical activity levels in individuals aged 15 years and older. The short-form IPAQ is a 7-day recall assessment method designed to capture activity across all domains of activity. This questionnaire was developed with input from international physical activity experts and has been applied to populations around the world.[60,61] The test–retest reliability of the short-form IPAQ has been reported to be $\rho = 0.76$ (95% CI 0.73–0.77), with reported criterion validity of $\rho = 0.30$ (95% CI 0.23–0.36).[61] Participants were categorised as *sufficiently active* if they had accumulated 3000 MET-minutes over 7 d, or 1500 MET-minutes of vigorous-intensity physical activity over 3 d or more. These cut-off points correspond to 30 min of moderate-intensity activity for 5 d or 20 min of vigorous-intensity physical activity for 3 d, above a basal level of 60 min of moderate-intensity activity each day.[61] For the purpose of estimating the cancer burden attributable to physical inactivity, we considered individuals not categorised as *sufficiently active* by the IPAQ as being exposed to inactivity. We also used a second definition of inactivity – the proportion of European individuals categorised as *sedentary* (<600 MET-minutes over 7 d) – to provide a more conservative estimate of the cancer burden attributable to physical inactivity. We used the average proportions, from across the 15 countries, of men and women not meeting the IPAQ *sufficiently active* criteria in Eurobarometer, Wave 58.2 for the PAR estimates for the whole of Europe.

Country- and gender-specific population-attributable risks (PARs) were estimated for the six cancer sites classified as *convincing*, *probably* or *possibly* associated with physical inactivity. Incidence estimates were not presented separately for colon cancer; hence we have used the estimated incidence of colorectal cancer in 2008 for these estimations. As such, our PAR estimates may be inflated for this site. We calculated PARs using the formula described by Levin[62] that includes the prevalence of exposure (i.e. the estimated proportion of

individuals not meeting the IPAQ *sufficiently active* criteria or the proportion categorised as *sedentary*) and the relative risk of developing a given type of cancer for individuals in the lowest versus highest (referent) physical activity category. The relative risk for each of the six cancer sites (colon, female breast, endometrial, lung, prostate and ovarian) was estimated as the mean of the fully adjusted point estimates presented by each study included in the recent reviews of physical activity and cancer risk.[6,19,21,26,34,63]

Gender-specific PARs and numbers of estimated preventable cancers are presented in Tables 1 and 2. For the estimates based on the proportion of individuals not meeting the IPAQ *sufficiently active* criteria, approximately 17% of male colon cancer cases, and possibly 21% of male lung and 14% of prostate cancer cases, could be prevented if sufficient levels of physical activity were achieved by all European men. Among women, 24% of endometrial, 20% of breast and 19% of colon cancer cases could theoretically be prevented if physical activity levels were sufficient. In addition, 24% of female lung and 15% of ovarian cancers might also possibly be attributed to physical inactivity. Overall, we estimate that 329,462 cases of cancer (approximately 19%) across the six sites diagnosed in Europe in 2008 could possibly have been prevented through higher levels of physical activity. The PAR estimates generated using the proportion of European individuals categorised as *sedentary* were somewhat lower, but still suggested that 165,747 cases (approximately 9%) of the colon, breast, endometrial, lung, prostate and ovarian cancers are preventable through increased physical activity. It is likely that the true number of preventable cancer cases lies somewhere between the two estimates generated from *insufficiently active* and *sedentary* individuals. Furthermore, our PAR estimates might have been different had we applied different assumptions to our PAR estimations, as in de Vries et al.[64] or had we accounted for the impact of effect modification on relative risk estimates.[65]

The PAR estimates presented in Tables 1 and 2 are based on relative risk estimates derived from the highest versus

Table 1 – Population-attributable risk (PAR) percent and estimated preventable cases (EPC) of cancers classified as convincingly (colon) and possibly (lung, prostate) associated with physical inactivity – males.

		Prevalence of inactivity (%)[a]	Colon		Lung		Prostate	
			PAR (%)	EPC[b]	PAR (%)	EPC	PAR (%)	EPC
Europe	*Insufficiently active*	64	17	38,717	21	62,420	14	52,464
	Sedentary	28	8	18,797	11	31,212	7	25,007
Austria	*Insufficiently active*	69	18	496	23	588	15	886
	Sedentary	32	9	256	12	312	7	449
Belgium	*Insufficiently active*	70	18	802	23	1286	15	1495
	Sedentary	35	10	439	13	724	8	804
Denmark	*Insufficiently active*	65	17	390	22	482	14	526
	Sedentary	23	7	155	9	198	5	204
Finland	*Insufficiently active*	64	17	226	21	324	14	654
	Sedentary	22	6	88	9	130	5	248
France	*Insufficiently active*	71	18	3750	23	5649	15	9916
	Sedentary	40	11	2299	15	3548	9	5987
Germany	*Insufficiently active*	54	15	5530	19	6501	12	8406
	Sedentary	24	7	2679	9	3231	6	4007
Great Britain	*Insufficiently active*	64	17	3488	22	5239	14	6491
	Sedentary	34	10	2001	13	3081	8	3667
Greece	*Insufficiently active*	57	15	294	20	1115	12	348
	Sedentary	28	8	157	11	609	7	183
Ireland	*Insufficiently active*	64	17	223	21	247	14	496
	Sedentary	29	8	112	11	127	7	243
Italy	*Insufficiently active*	69	18	5110	23	6427	15	5888
	Sedentary	32	9	2621	12	3396	7	2964
Luxembourg	*Insufficiently active*	54	15	23	19	34	12	34
	Sedentary	19	6	9	8	14	5	13
Netherlands	*Insufficiently active*	52	14	877	18	1199	11	1212
	Sedentary	20	6	371	8	521	5	503
Portugal	*Insufficiently active*	63	17	650	21	545	14	681
	Sedentary	28	8	318	11	274	7	327
Spain	*Insufficiently active*	66	17	2926	22	4503	14	3634
	Sedentary	27	8	1328	10	2111	6	1616
Sweden	*Insufficiently active*	72	19	556	24	422	15	1586
	Sedentary	31	9	268	12	210	7	748

RR for colon cancer derived from 52 studies = 0.76[6]; RR for lung cancer derived from nine studies = 0.70[26]; RR for prostate cancer derived from 27 studies = 0.80.[63]

[a] Physical activity estimates derived from the Eurobarometer study for 15 European countries.[58]

[b] Estimated cancer incidences for 2008 from Ferlay et al.[59] for all of Europe and for individual countries. Note that the estimated preventable cases for colon cancer are based on the estimated incidence of colorectal cancer in 2008.

Table 2 – Population-attributable risk (PAR) percent and estimated preventable cases (EPC) of cancers classified as convincingly (colon), probably (breast, endometrial) and possibly (ovarian, lung) associated with physical inactivity – females.

		Prevalence of inactivity (%)[a]	Colon		Breast		Endometrial		Ovarian		Lung	
			PAR (%)	EPC[b]	PAR (%)	EPC	PAR	EPC	PAR (%)	EPC	PAR (%)	EPC
Europe	*Insufficiently active*	74	19	38,729	20	83,353	24	19,892	15	9882	24	24,005
	Sedentary	34	10	19,802	10	42,837	13	10,496	7	4929	13	12,667
Austria	*Insufficiently active*	79	20	460	21	1090	25	252	16	111	25	346
	Sedentary	39	11	253	12	603	14	143	8	60	14	196
Belgium	*Insufficiently active*	80	20	728	21	2030	25	351	16	146	25	407
	Sedentary	45	12	452	13	1264	16	223	10	89	16	259
Denmark	*Insufficiently active*	67	17	378	18	760	22	158	14	75	22	450
	Sedentary	21	6	135	7	273	8	59	5	26	8	167
Finland	*Insufficiently active*	71	18	231	19	781	23	189	14	66	23	159
	Sedentary	26	8	96	8	325	10	81	6	26	10	68
France	*Insufficiently active*	81	20	3734	21	10,791	26	1575	16	704	26	2101
	Sedentary	46	13	2336	13	6781	16	1011	10	432	16	1349
Germany	*Insufficiently active*	65	17	5525	18	11,466	22	2372	13	1164	22	3265
	Sedentary	24	7	2277	7	4751	9	1012	5	467	9	1393
Great Britain	*Insufficiently active*	78	20	3338	21	9364	25	1570	15	1077	25	4058
	Sedentary	41	11	1944	12	5479	15	940	9	613	15	2430
Greece	*Insufficiently active*	69	18	295	19	911	23	246	14	146	23	246
	Sedentary	37	10	173	11	535	14	148	8	84	14	148
Ireland	*Insufficiently active*	78	20	201	21	561	25	87	15	62	25	215
	Sedentary	40	11	114	12	321	15	51	9	34	15	126
Italy	*Insufficiently active*	79	20	4628	21	9914	25	1764	16	796	25	2147
	Sedentary	39	11	2536	12	5461	14	997	8	426	14	1213
Luxembourg	*Insufficiently active*	72	19	28	19	66	24	14	14	7	24	19
	Sedentary	32	9	14	10	33	12	7	7	3	12	10
Netherlands	*Insufficiently active*	60	16	864	17	2154	20	384	12	127	20	775
	Sedentary	19	6	308	6	772	8	142	4	44	8	286
Portugal	*Insufficiently active*	70	18	521	19	1001	23	194	14	74	23	155
	Sedentary	31	9	256	9	494	12	99	7	35	12	79
Spain	*Insufficiently active*	83	21	2489	22	4810	26	1160	16	520	26	828
	Sedentary	35	10	1195	10	2323	13	578	8	243	13	412
Sweden	*Insufficiently active*	82	21	585	21	1399	26	359	16	123	26	450
	Sedentary	35	10	283	10	680	13	180	8	58	13	226

RR for breast cancer derived from 62 studies = 0.75[19]; RR for colon cancer derived from 52 studies = 0.76[6]; RR for endometrial cancer derived from 18 studies = 0.70[21]; RR for ovarian cancer derived from 12 studies = 0.81[34]; RR for lung cancer derived from nine studies = 0.70.[26]

[a] Physical activity estimates derived from the Eurobarometer study for 15 European countries.[58]

[b] Estimated cancer incidences for 2008 from Ferlay et al.[59] for all of Europe and for individual countries. Note that the estimated preventable cases for colon cancer are based on the estimated incidence of colorectal cancer in 2008.

the lowest category of physical activity. The PARs may therefore be an optimistic estimate of the number of cancer cases that could be prevented, as they presume exercise at the upper end of the physical activity range. Another inherent limitation is that physical activity categories differ significantly between studies. Hence, the strength of the point estimates used to generate the average relative risk used in the PAR calculations may be dependent somewhat on cut-offs used to define the most and the least active participants.

4. Hypothesised biological mechanisms

For those cancers that are convincingly, probably or possibly related to physical inactivity, an understanding of the underlying biological mechanisms adds plausibility to the association, identifies specific targets for cancer prevention and helps guide future public health recommendations. Across the six cancer sites discussed earlier in this review, numerous biological pathways have been hypothesised and in some cases tested in randomised controlled trials (RCTs).[2,3,66–68] Table 3 highlights some commonly proposed mechanisms organised according to the level of epidemiological evidence currently supporting their associations with physical activity. Sex hormones have been classified twice to reflect the differing evidence across population sub-groups and cancer sites.

To become firmly established in a causal pathway, each proposed mechanism must relate significantly both to cancer risk and physical activity. It is clear from Table 3 that more research is needed, ideally from RCTs, to better understand the effects of different doses and types of physical activity on the various biological pathways. RCTs help to demonstrate the ability of physical activity to produce not only statistically significant changes but also clinically meaningful changes in candidate biomarker levels. It is possible that exercise alone cannot alter a single biological pathway to the extent that is needed to significantly lower cancer risk. In the context of

Table 3 – Potential biological mechanisms relating physical activity to cancer risk[a].

Proposed mechanisms	Possible effects of physical activity	Cancer sites possibly associated with the proposed mechanism[b]
Stronger evidence for an effect of physical activity		
Body fat	Reduces body fat and consequently lowers levels of adipokines, inflammatory markers, oestrogens (post-menopause) and testosterone; improves insulin sensitivity, increases sex hormone binding globulin (SHBG) levels	Colon, postmenopausal breast, endometrium, ovaries
Insulin resistance	Improves insulin sensitivity and lowers plasma insulin, C-peptide and glucose levels on account of: reduced body fat, increased skeletal muscle mass, increased glucose transport into muscle and decreased fatty acid synthesis	Colon, breast, endometrium, ovaries, prostate
Improved pulmonary function	Lowers concentration of carcinogenic material in lungs Shortens exposure time between lung tissue and carcinogenic agents	Lung
Sex hormones	Post-menopause: body fat loss decreases aromatase and 17β-hydroxysteroid dehydrogenase levels within adipose tissue; may lower oestrone, estradiol and testosterone synthesis Hepatic synthesis of SHBG increases as a result of lowered insulin levels; decreases estradiol and testosterone bioavailability	Breast, endometrium, ovaries
Emerging, conflicting or limited evidence for an effect of physical activity		
Vitamin D	Associated with higher 25-hydroxyvitamin D blood levels, but the mechanism is unclear (e.g. surrogate for sun exposure, or due to diet, less body fat)	Colon, breast
Insulin-like growth factors (IGF)	Might decrease IGF-1 and increase IGFBP-3 (the main binding protein for IGF-1). However, most epidemiological evidence does not support an effect	Colon, premenopausal breast, endometrium, ovaries, prostate, lung
Sex hormones	Pre-menopause: ovarian production of oestrogens may decrease; very high levels of physical activity (or an energy deficit) could lower lifetime oestrogen exposure by delaying menarche, causing menstrual dysfunction, reducing the number of ovulatory cycles. However, findings in studies of non-athletes are inconsistent Men: effects on androgen levels are unclear, but dihydroxytestosterone, a testosterone metabolite, may be increased. Few studies have addressed the effects of long-term, moderate-intensity exercise in men	Breast, endometrium, ovaries, prostate
Adipokines	Decreases body fat, the main source of circulating leptin May increase adiponectin levels by decreasing interleukin-6 (IL-6) and TNF-α, which inhibit its expression, but possibly only with significant weight loss	Colon, breast, endometrium, prostate, lung
Chronic low-grade inflammation	May decrease levels of inflammatory markers C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), partly through fat loss. However, very few long-term exercise intervention studies have tested this hypothesis and anti-inflammatory mechanisms have not been elucidated	Most cancers
Immune function	May improve the innate (e.g. natural killer cell number/function) and acquired immune responses to better recognise and eliminate cancerous cells Effects of long-term, moderate-intensity exercise in at-risk human populations are not well understood	Most cancers
Oxidative stress, antioxidant defence and DNA repair	May reduce oxidative stress (perhaps only with improved aerobic fitness), increase antioxidant enzymes, e.g. superoxide dismutase, and/or enhance DNA repair systems	Most cancers
Prostaglandins	May inhibit synthesis of prostaglandin E_2 (PGE_2– promotes colon cancer) and/or stimulate prostaglandin $F_{2\alpha}$ synthesis ($PGF_{2\alpha}$– opposes PGE_2). However, there were no effects on colon mucosal prostaglandin levels in a 12-month moderate-intensity exercise RCT	Colon
Gastrointestinal transit time	Increases gut motility and may decrease transit time; less interaction between colon mucosa and carcinogens. However, changes are probably of insufficient magnitude to alter risk significantly	Colon

[a] Table content is based on reviews of the proposed mechanisms[2,3,66–68,75,99–101] and evidence from randomised controlled trials.[8,69,102–107]

[b] Table is limited to six cancers for which the current epidemiological evidence suggests convincing or possible associations with physical activity. Most of the above mechanisms are hypothesised to increase cancer risk and are unconfirmed.

postmenopausal breast cancer and oestrogens, which are causally related, moderate to vigorous exercise sustained over 12 months has decreased total estradiol levels by 11–14% with concurrent body fat loss in postmenopausal women.[69–71] Yet a substantially greater difference in serum estradiol levels, perhaps in the order of 100% (i.e. seven to nine times higher than in exercise RCTs), lowers postmenopausal breast cancer risk by 29% on average in prospective observational studies.[72] The simultaneous influence of exercise on multiple biological pathways, however, could still theoretically produce clinically important decreases in cancer risk. Unfortunately aetiological studies to date have largely focused on isolated hypothesised causal pathways and so the cancer risk reduction from a multifaceted physical activity effect (e.g. lowered oestrogen levels *and* insulin levels *and* inflammatory markers in relation to postmenopausal breast cancer risk) is unknown. Hence, there is also a need for prospective aetiological studies in humans to clarify which of the mechanisms in Table 3 – individually or perhaps in combination – is associated with cancer risk; particularly with respect to adipokines,[73,74] vitamin D[75] and mechanisms surrounding innate immunity, inflammatory factors and oxidative stress,[76,77] which have been studied in this context only relatively recently.

The fact that several proposed mechanisms are interrelated, and that additive, opposing and even synergistic effects may occur, adds another level of complexity when research is conducted to disentangle the effects of single biological mechanisms. Possible biomarkers of risk such as insulin, insulin-like growth factor-1 (IGF-1), leptin, tumour necrosis factor-alpha (TNF-α), oestrogens and vitamin D may each affect cancer risk directly, for instance, by increasing cell proliferation and decreasing apoptosis in certain cell types,[73,75,78–80] but they may also influence risk indirectly through other pathways. Leptin, for example, induces the aromatase enzyme, thereby increasing oestrogen levels, and is elevated with insulin resistance and obesity.[73] Adiponectin is anti-angiogenic, anti-mitogenic, anti-inflammatory, promotes insulin sensitivity and is lowered with obesity.[74] Hence, the ratio of adiponectin:leptin is now a hypothesised risk factor for postmenopausal breast cancer.[81] For each cancer there may be one pivotal mechanism that underlies and drives several other related pathways.[82] Identifying this mechanism may be the key to informing the optimal exercise prescription for cancer prevention.

The biological pathways outlined in Table 3 are either emerging as potentially important, are currently being investigated in prospective epidemiological studies, or have been studied extensively in the past. Additional mechanisms (e.g. relating to carcinogen activation and detoxification[68,83] or intracellular signalling pathways[84]) may also be important; however, insufficient epidemiological research has been conducted on these mechanisms to assess their relative importance in the association between physical activity and cancer. Moreover, it is important to recognise that effect modification by other factors likely affects these pathways as well. A host of genetic sub-types, for example, could theoretically alter individual responses to the biomarkers proposed in Table 3, or to physical activity. Future mechanistic studies may need to account for effect modification both in their design and in the statistical analyses.

5. Limitations of the existing evidence and future research directions

Several limitations exist in this field of cancer research that need to be considered, particularly when articulating new research directions. These include the difficulty in assessing physical activity, the limited number of controlled exercise intervention trials that have been specifically designed to examine the underlying biological mechanisms and the complete lack of randomised controlled trials of exercise for cancer prevention.

Inherent in observational epidemiological studies of physical activity and cancer are the limitations in measuring physical activity because of the complexity of this exposure; the difficulty in estimating an integrated measurement of physical activity that includes all types, parameters and time periods in life when physical activity was performed; and the abilities of study participants to report their activities without bias. A wide variety of subjective and objective physical activity measurement methods have been developed; not all have been routinely tested for reliability and validity and not all systematically assess all components of physical activity. The lack of standard definitions of physical activity as well as the complete lack of harmonisation in these assessment methods across studies has also resulted in difficulty comparing results from different studies. Furthermore, even if physical activity is measured with reliability and validity, the range of physical activity in some study populations has not been sufficiently wide to assess the effect of high doses of physical activity on cancer risk. Effect modification by tumour type and population sub-groups likely exists, but has been infrequently examined for most cancer sites.

Biological mechanisms involved in the pathways between physical activity and cancer remain poorly understood. There are also difficulties in disentangling the effects of physical activity from weight loss, and only limited research effort has focused on this topic. Some recent exercise and diet intervention trials (e.g. the Nutrition and Exercise in Women Trial; NEW Trial) conducted by McTiernan and colleagues at the Fred Hutchinson Cancer Research Centre[85] are examining how weight loss influences potential biomarkers of cancer risk and may help elucidate the relative importance of physical activity versus weight loss in cancer aetiology.

A need to move from observational studies to intervention trials of exercise and cancer risk has been recognised over this past decade.[4,86] Recently, a small number of RCTs conducted in the Netherlands, Canada and the United States have tested the effects of exercise on proposed biomarkers of risk[69,87–90] with results demonstrating the direct effect of physical activity on endogenous sex steroids, insulin resistance, inflammatory markers, adiposity levels as well as other mechanisms. This area of research has particular potential to elucidate the exact doses and types of physical activity that may be most appropriate in reducing cancer risk. Finally, an emerging area of interest in physical activity and cancer risk that has only received minimal attention to date is the effect of sedentary behaviour on cancer risk. Sedentary behaviour is defined as any activity that expends 1.5 METs per hour or less, and is characterised by prolonged sitting time.[91]

The limited research to date has linked sedentary behaviour with ovarian,[35,36] endometrial[23,25] and colorectal cancer development.[92] Sedentary behaviour is independently associated with obesity[93–95] and insulin resistance;[96–98] hence it is biologically plausible that sedentary behaviour may be a contributing factor to some types of cancer.

6. Conclusion

The quantity and quality of research on physical activity and cancer have increased exponentially in the past 20 years with a large body of evidence that is now becoming established and increasingly recognised worldwide. Physical activity is recognised as a modifiable lifestyle risk factor for most chronic diseases, including cancer, by international agencies.[1–3] Evidence for the underlying biological mechanisms involved in the pathways between physical activity and cancer risk is also emerging and can be used to refine the public health recommendations on the type, dose and timing of physical activity that is required to reduce cancer risk. At present, these recommendations are for 30–60 min of at least moderate-intensity activity for at least 5 d per week.[1–3] Given that between 9% and 19% of cancers occurring in Europe currently could be attributed to lack of sufficient physical activity, there is a strong rationale for firmly supporting physical activity as an integral component of cancer prevention programs.

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Conflict of interest statement

None declared.

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