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Review

Cancer Epidemiology, Biomarkers & Prevention

Sedentary Behavior and Cancer: A Systematic Review of the Literature and Proposed Biological Mechanisms

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Abstract

Background: Sedentary behavior (prolonged sitting or reclining characterized by low energy expenditure) is associated with adverse cardiometabolic profiles and premature cardiovascular mortality. Less is known for cancer risk. The purpose of this review is to evaluate the research on sedentary behavior and cancer, to summarize possible biological pathways that may underlie these associations, and to propose an agenda for future research.

Methods: Articles pertaining to sedentary behavior and (*a*) cancer outcomes and (*b*) mechanisms that may underlie the associations between sedentary behavior and cancer were retrieved using Ovid and Web of Science databases.

Results: The literature review identified 18 articles pertaining to sedentary behavior and cancer risk, or to sedentary behavior and health outcomes in cancer survivors. Ten of these studies found statistically significant, positive associations between sedentary behavior and cancer outcomes. Sedentary behavior was associated with increased colorectal, endometrial, ovarian, and prostate cancer risk; cancer mortality in women; and weight gain in colorectal cancer survivors. The review of the literature on sedentary behavior and biological pathways supported the hypothesized role of adiposity and metabolic dysfunction as mechanisms operant in the association between sedentary behavior and cancer.

Conclusions: Sedentary behavior is ubiquitous in contemporary society; its role in relation to cancer risk should be a research priority. Improving conceptualization and measurement of sedentary behavior is necessary to enhance validity of future work.

Impact: Reducing sedentary behavior may be a viable new cancer control strategy. *Cancer Epidemiol Biomarkers Prev; 19(11); 2691–709. ©2010 AACR.*

Introduction

There is considerable epidemiologic research suggesting that physical activity can reduce the risk and progression of several cancers (1-3). Emerging evidence suggests that sedentary behavior has deleterious health consequences that are distinct from the beneficial effects of moderate- to vigorous-intensity physical activity (4, 5). A unique sedentary behavior physiology, with different biological processes from traditionally understood exercise physiology, has been hypothesized (5). Hence, it is possible that sedentary behavior could independently contribute to cancer risk.

Sedentary behavior describes activities of low (≤1.5 metabolic equivalents) energy expenditure (6, 7). It is characterized by prolonged sitting or lying down and the absence of whole-body movement, for example, watching television or working at a computer (6). Sedentary behavior is not a synonym for physical inactivity, which describes the absence of health-enhancing physical activity in everyday life (8). It is thus possible for an individual to achieve or exceed physical activity recommendations (30 minutes or more of moderate-to vigorous-intensity activity, 5 days per week), yet spend the majority of his or her waking hours sitting (4). Within epidemiologic and health behavior research, measurement of adults' sedentary behavior has typically focused on television viewing time, one of the most frequently reported leisure-time pursuits (9).

A number of epidemiologic studies have shown sedentary behavior to be independently associated with chronic disease–related risk factors such as central adiposity, elevated blood glucose and insulin, and other cardiometabolic biomarkers in healthy adults (10-17). Such metabolic attributes are hypothesized to be operative in the development and progression of cancer. It is therefore biologically plausible that sedentary behavior may be a contributing factor to some types of cancer. Endogenous sex hormones, inflammation, and vitamin D also present as plausible biological pathways by which sedentary behavior might additionally contribute to cancer risk (18).

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The purpose of this report is 3-fold: (*a*) to systematically review studies examining associations of sedentary behavior with cancer risk or health outcomes in cancer survivors; (*b*) to describe and review evidence on the biological pathways that may underlie such associations; and (*c*) to formulate recommendations for future research on sedentary behavior and cancer.

Materials and Methods

Search strategy

A comprehensive literature search strategy was developed in consultation with a librarian from the Tom Baker Cancer Knowledge Centre (Calgary, AB, Canada). Ovid (MEDLINE, EMBASE, PsycINFO), and Web of Science (Science Citation Index Expanded, Social Sciences Citation Index, Arts and Humanities Citation Index, Conference Proceedings Citation Index-Science, Conference Proceedings Citation Index-Social Science and Humanities) databases were searched for publications up to June 2010. Articles on sedentary behavior were found to be cross-indexed under several subject terms: "physical activity," "exercise," "motor activity," and "health behavior." These subject terms were combined with the keywords "sedentary behavior," "sitting," "television," and "TV" to form the search strategy for identifying articles specifically pertaining to sedentary behavior (prolonged sitting or lying down).

To address the first aim of this report, the keywords "cancer," "neoplasm," and "tumor" were included in the search to identify articles concerning incident cases of cancer, cancer mortality, and health outcomes potentially related to prognosis in cancer survivors. To identify literature pertaining to proposed biological pathways, keywords associated with adiposity (adiposity, overweight, obesity, weight gain), sex hormones (sex hormones, estrogen, androgen, sex hormone binding globulin), metabolic dysfunction (insulin, glucose, insulin resistance, c-peptide, insulin like growth factor), inflammation (C-reactive protein, interleukin-6, tumor necrosis factor-α, leptin, adiponectin, resistin) or vitamin D (vitamin D, 25-hydroxyvitamin D) were added. The author reviewed the titles and abstracts of all articles identified by the literature search to assess their relevance.

The reference lists of articles identified by the literature search were also screened for additional relevant articles, as were the reference lists of several recent review articles on the health effects of sedentary behavior (4-6, 19, 20). The early-view and in-press articles from journals that had published papers meeting the review criteria were also examined.

Inclusion and exclusion criteria

Inclusion criteria for retrieved articles included being written in English, published between 1980 and June 2010, and composed of nonpregnant adult study participants (not children or adolescents). To be included in the review, sedentary behavior had to be assessed as a distinct predictor variable independent from physical activity (i.e., sedentary was not simply defined as no reported participation in physical activity). Studies in which the term "sedentary" was used to describe an activity level assigned based on participants' job title (usually from industry and occupation codes) were excluded on the basis that this method of categorization may more accurately reflect a lack of physical labor within their occupation rather than a high volume of prolonged sitting. Studies where participants reported their level of occupational sitting were included.

Data extraction

Where multiple articles from the same study were found, data were extracted from the most recent article (cohort studies) or the original article (case-control studies). Methodologic details from each article were collected, including information about the study design, sample, and measures of sedentary behavior used. The risk reductions extracted from each study represent the highest versus lowest category of sedentary behavior assessed. Study results were defined null if the relative risks (RR) or odds ratios (OR) fell between 0.9 and 1.1, inclusive. If the lower limit of the 95% confidence intervals (95% CI) was ≥0.95, the results were considered of borderline statistical significance. Average risk reductions (the unweighted mean of the point estimates) were calculated to allow comparisons across cancer sites. Where more than one type of sedentary behavior was assessed, the point estimate for total sitting time (or the sedentary behavior that accounted for the greatest amount of time) was used for the average risk reductions.

Results

Literature search results

Figure 1 describes the number of articles identified at each stage of the literature search strategy. The majority of articles retrieved by the Ovid and Web of Science databases were rejected on the basis that "sedentary" was a term used to denote no participation in moderate- to vigorous-intensity physical activity.

For the review on sedentary behavior and cancer, 18 relevant articles were identified (21-38). For sedentary behavior and adiposity, 76 articles originating from 62 studies were selected for review (10, 12, 13, 15-17, 39-103). The literature search on sedentary behavior and biological mechanisms identified 17 articles from 11 studies relating to sedentary behavior and metabolic dysfunction (10-14, 17, 52, 84, 89, 101, 103-109), and one article each for sedentary behavior and sex hormones (109), inflammation (107), and vitamin D (110).

Sedentary behavior and cancer

The study design, population characteristics, methods of assessing sedentary behavior, and the main results (fully adjusted risk estimates for highest versus lowest level of sedentary behavior) of each of the 18 studies

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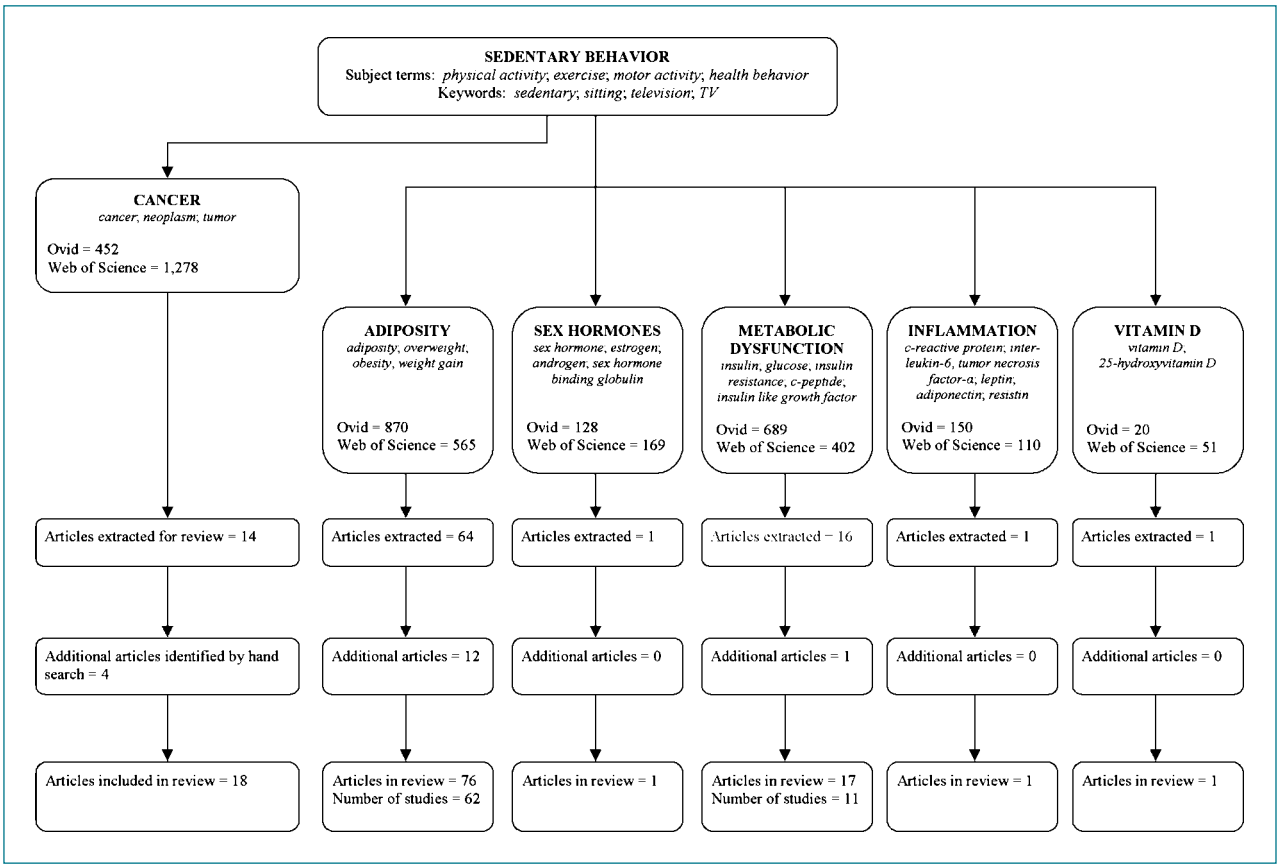

Figure 1. Literature search strategy.

examining the association between sedentary behavior and cancer outcomes are described in Table 1. Ten studies quantified the association between sedentary behavior and cancer risk (21, 23-26, 28-31, 33, 35), whereas four reported the relationship between sedentary behavior and cancer mortality (22, 27, 32, 34). Three articles examined the association of sedentary behavior with adiposity or weight gain in cancer survivors (36-38).

Sedentary behavior and cancer risk. Six of the 11 cancer risk studies were prospective cohort studies (23, 25, 26, 29-31), four were case-control studies (24, 28, 33, 35), and one was a randomized controlled trial (21). The association between sedentary behavior and cancer risk was investigated in four studies of endometrial cancer (23-25, 31): three of colorectal cancer (21, 26, 33), two of ovarian cancer (30, 35), and one each of breast (28) and prostate (29) cancer.

Statistically significant, positive associations between sedentary behavior and cancer were found in 8 of the 11 studies (21, 23, 24, 26, 29, 30, 33, 35). An additional study had a borderline statistically significant, positive association (25), and one observed a nonstatistically significant risk increase (31). One study observed a nonstatistically significant cancer risk reduction among the women who reported watching the most television (28). The greatest risk increases were found for colorectal cancer (average increase 78%; refs. 21, 26, 33), followed by ovarian cancer (66%; refs. 30, 35), prostate (39%; ref. 29), and endometrial (34%; refs. 23-25, 31) cancer. For breast cancer, the highest weekday television-viewing category was associated with an 18% risk reduction for premenopausal women; however, this risk reduction was not statistically significant. The associations of weekend television viewing with breast cancer risk in premenopausal women, and weekday and weekend television viewing with postmenopausal breast cancer risk, were null (28).

The randomized controlled trial had a sample of 29,133 male smokers (21), whereas the prospective cohort studies had large, population-representative samples (21, 23, 25, 26, 29-31). Three of the case-control studies included in this review were hospital based (28, 33, 35); the other case-control study was population based (24). There was considerable variation in sample sizes in the case-control studies: The breast cancer case-control study recruited 1,866 cases and 1,873 controls (28), whereas the colorectal cancer case-control study had 180 cases and 180 controls (33).

The sedentary behavior exposure measures used in the studies included single items assessing nonoccupational sitting time (23, 30, 31), total sitting time (25, 26), or television viewing time (25, 26, 33). Two studies included

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Table 1. Studies investigating the associations of sedentary behavior and cancer

Authors	Design	Sample	Outcome	Measure of sedentary behavior	Results	Adjustment for confounding
Sedentary behavior and breast cancer risk						
Mathew et al., 2009 (28)	Case-control study.	1,866 cases treated at one of four hospitals in South India; 1,873 controls matched by 5-y age group and place of residence (urban/rural).	Histologically confirmed incident primary breast cancer.	Time spent watching TV during weekdays and weekends. Patients were asked to report TV time from the year preceding diagnosis.	No statistically significant associations between TV time and breast cancer in either premenopausal or postmenopausal women. Weekday TV ≥180 vs <60 min/d OR (premenopausal), 0.94 (95% CI, 0.62-1.45); OR (postmenopausal), 0.82 (95% CI, 0.51-1.35). Weekend TV ≥180 vs <60 min/d OR (premenopausal), 0.90 (95% CI, 0.61-1.34); OR (postmenopausal), 1.01 (95% CI, 0.64-1.59).	Age, locality, religion, marital status, education, socioeconomic status, residence status, BMI, waist and hip sizes, parity, age at first childbirth, duration of breast-feeding, physical activity.
Sedentary behavior and colorectal cancer risk						
Howard et al., 2008 (26)	Prospective cohort study.	300,673 participants from the NIH-AARP Diet and Health Study, ages 51-72 y at questionnaire administration.	4,722 incident colorectal cancers identified through linkage to 11 state cancer registries.	Predefined categories for (*a*) time spent watching TV or videos and (*b*) sitting during a typical 24-h period in the past 12 mo.	For men, watching TV ≥9 vs <3 h/d associated with increased risk of colorectal cancer (RR, 1.56; 95% CI, 1.11-2.20). Total sitting duration (≥9 vs <3 h/d; RR, 1.22; 95% CI, 0.96-1.55). For women, watching TV ≥9 vs <3 h/d associated with borderline increased risk of colorectal cancer (RR, 1.45; 95% CI, 0.99-2.13). Total sitting duration (≥9 vs <3 h/d; RR, 1.23; 95% CI, 0.89-1.70).	Age; smoking; alcohol consumption; education; race; family history of colon cancer; total energy intake; energy-adjusted intakes of red meat, calcium, whole grains, fruits, and vegetables; menopausal hormone therapy (women); BMI; physical activity.

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Table 1. Studies investigating the associations of sedentary behavior and cancer (Cont'd)

Authors	Design	Sample	Outcome	Measure of sedentary behavior	Results	Adjustment for confounding
Colbert et al., 2001 (21)	Randomized controlled trial.	29,133 men from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study, who smoked ≥5 cigarettes/d and were ages 50-69 y at baseline.	152 colon and 104 rectal cancers identified through the Finnish Cancer Registry.	Predefined categories for (*a*) occupational activity (from mainly sitting to heavy physical work) and (*b*) usual leisure-time activity (sedentary, e.g., watching TV to heavy fairly regularly, e.g., running) in the past 12 mo.	Compared with men who reported a lifetime of moderate/heavy work, men whose occupation involved mainly sitting had a significantly increased risk of colon (RR, 2.22; 95% CI, 1.28-3.85) and rectal (RR, 2.00; 95% CI, 1.03-3.85) cancer. Men whose leisure time was mostly sedentary, compared with active, also had elevated but nonsignificantly risk (colon RR, 1.22; 95% CI, 0.88-1.69; rectal RR, 1.08; 95% CI, 0.73-1.59).	Colon cancer: age, supplement group, BMI, cigarettes per day. Rectal cancer: age, supplement group.
Steindorf et al., 2000 (33)	Case-control study.	180 cases treated at a Polish hospital, and 180 age- and sex-matched controls selected from patients without cancer or digestive tract disorders.	Histologically confirmed incident cases of colon and rectal cancer.	Time spent watching TV in leisure time (h/d). Categorized as tertiles.	TV time was positively associated with increased risk of colorectal cancer (OR, 2.22; 95% CI, 1.19-4.17 for <1.14 h/d vs ≥2 h/d).	Education, total energy intake.
Sedentary behavior and endometrial cancer risk						
Friedenreich et al., 2010 (24)	Case-control study.	542 cases identified through the Alberta Cancer Registry; 1,032 age-matched controls recruited from the community.	Incident, histologically confirmed invasive cases of endometrial cancer.	Lifetime occupational sitting time (h/wk/y) assessed by total lifetime physical activity questionnaire.	Occupational sitting time was associated with increased risk of endometrial cancer (OR, 1.02; 95% CI, 1.00-1.04 for each h/wk/y increase in sitting time; OR, 1.11; 95% CI, 1.01-1.22 for 5 h/wk/y increase).	Age, BMI, waist circumference, age at menarche, hypertension, number of pregnancies ≥20 wk gestation.

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Table 1. Studies investigating the associations of sedentary behavior and cancer (Cont'd)

Authors	Design	Sample	Outcome	Measure of sedentary behavior	Results	Adjustment for confounding
Gierach et al., 2009 (25)	Prospective cohort study.	70,351 women from the NIH-AARP Diet and Health Study, ages 51-72 y at questionnaire administration.	1,052 incident endometrial cancers identified through linkage to 11 state cancer registries.	Predefined categories for (*a*) time spent watching TV or videos and (*b*) sitting during a typical 24-h period in the past 12 mo.	Sitting time ≥7 vs <3 h/d associated with borderline increased risk of endometrial cancer (RR, 1.23; 95% CI, 0.96-1.57). TV was not significantly associated with endometrial cancer risk.	Age, race, smoking, parity, oral contraceptive use, age at menopause, hormone therapy use, BMI, vigorous physical activity.
Patel et al., 2008 (31)	Prospective cohort study.	42,672 women from the CPS-II Nutrition Cohort (mean age 63 at baseline).	466 endometrial cancer cases identified by self-report (verified by state cancer registries or medical records) or through National Death Index.	Predefined categories for time spent sitting (watching TV, reading etc) outside of job.	Sitting time not associated with statistically significant increased risk of endometrial cancer in the fully adjusted model. Sitting time ≥6 vs <3 h/d; RR, 1.18 (95% CI, 0.87-1.59).	Age, BMI, oral contraceptive use, parity, age at menarche, age at menopause, postmenopausal hormone therapy use, personal history of diabetes, smoking, total energy intake.
Friberg et al., 2006 (23)	Prospective cohort study.	33,723 women from the Swedish Mammography Cohort, ages 50-83 y at baseline.	199 incident endometrial cancers identified through national and regional cancer registries.	Predefined categories for time spent per day watching TV/sitting.	Watching TV/sitting ≥5 vs <5 h/d associated with increased risk of endometrial cancer (RR, 1.66; 95% CI, 1.05-2.61.	Age, parity, history of diabetes, education, total fruit and vegetable intake, BMI, oral contraceptive use, postmenopausal hormone use, age at menarche, age at menopause, smoking, total energy intake, leisure-time physical activity.
Sedentary behavior and ovarian cancer risk						
Patel et al., 2006 (30)	Prospective cohort study.	59,695 women from the CPS-II Nutrition Cohort, ages 50-74 y baseline.	314 ovarian cancer cases identified by self-report (verified by state cancer registries or medical records) or through the National Death Index.	Predefined categories for time spent sitting (watching TV, reading etc) outside of job.	Sitting time ≥6 vs <3 h/d associated with increased risk of ovarian cancer (RR, 1.55; 95% CI, 1.08-2.22).	Age, race, BMI, oral contraceptive use, parity, age at menopause, age at menarche, family history of breast and/or ovarian cancer, simple hysterectomy, postmenopausal hormone replacement therapy. Additional adjustment for recreational physical activity (data not shown).

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Table 1. Studies investigating the associations of sedentary behavior and cancer (Cont'd)

Authors	Design	Sample	Outcome	Measure of sedentary behavior	Results	Adjustment for confounding
Zhang et al., 2004 (35)	Case-control study.	254 women under 75 y recently treated for ovarian cancer in hospitals in Hangzhou, China, and 652 age-matched controls.	Epithelial ovarian cancer histologically diagnosed in past 3 y.	Number of hours spent in variety of sitting tasks 5 y ago recalled. Calendars were used to assist recall. Structured questionnaire based on validated Hawaii Cancer Research Survey and Australian Health Survey.	Watching TV >4 vs <2 h/d associated with increased risk of ovarian cancer (OR, 3.39; 95% CI, 1.0-11.5). Total sitting duration (>10 vs <4 h/d; OR, 1.77; 95% CI, 1.0-3.1) and sitting at work (>6 vs <2 h/d; OR, 1.96; 95% CI, 1.2-3.2) also significantly associated with ovarian cancer risk.	Age, locality, education, family income, BMI, smoking, alcohol consumption, tea consumption, physical activity, marital status, menopausal status, parity, oral contraceptive use, tubal ligation, hormone replacement therapy, ovarian cancer in first-degree relatives, total energy intake.
Sedentary behavior and prostate cancer risk						
Orsini et al., 2009 (29)	Prospective cohort study.	Population-based sample of 45,887 Swedish men, ages 45-79 y at baseline.	2,735 incident prostate cancers identified through national and regional cancer registries, and 190 deaths identified through the Swedish Register of Death Causes.	Predefined categories for occupational activity levels (from mostly sitting to heavy manual labor).	Compared with men who reported a lifetime of heavy manual labor, men whose occupation involved mainly sitting had a 40% increased risk of prostate cancer (OR, 1.39; 95% CI, 1.11-1.75). Association with prostate cancer death was nonsignificant.	Lifetime walking and bicycling levels, waist-hip ratio, height, diabetes, alcohol consumption, smoking status, education, total energy intake, consumption of dairy products, red meat consumption, parental history of prostate cancer.
Sedentary behavior and cancer mortality						
Wijndaele et al., in press (34)	Prospective cohort study.	13,197 English adults (mean age 62 y) from the EPIC-Norfolk cohort.	1,270 deaths (including 570 from cancer) identified through the Office of National Statistics (United Kingdom). Mean follow-up 10 y.	Hours per week spent watching TV and videos over the past year.	No significant association between TV-viewing time and cancer mortality (HR, 1.04; 95% CI, 0.98-1.10 for each hour increase in TV time). TV time was associated with increased risk of all-cause mortality (HR, 1.05; 95% CI, 1.01-1.09 for each hour increase) and cardiovascular mortality (HR, 1.08; 95% CI, 1.01-1.16).	Age, gender, education level, smoking status, alcohol consumption, hypertension medication, dyslipidemia medication, baseline history of diabetes, family history of cardiovascular disease, family history of cancer, physical activity energy expenditure.

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Table 1. Studies investigating the associations of sedentary behavior and cancer (Cont'd)

Authors	Design	Sample	Outcome	Measure of sedentary behavior	Results	Adjustment for confounding
Patel et al., 2010 (32)	Prospective cohort study.	123,216 U.S. adults (ages 50-74 y at baseline) from the American Cancer Society CPS-II Nutrition Cohort.	19,230 deaths (including 6,989 cancer deaths) identified through the National Death Index; 14 y follow-up.	Predefined categories for time spent sitting outside of work, on an average day.	Sitting ≥6 vs 0 to <3 h/d associated with increased risk of cancer death for women (RR, 1.30; 95% CI, 1.16-1.46), *P* for trend < 0.0001. No association between sitting time and cancer mortality observed for men (RR, 1.04; 95% CI, 0.94-1.15).	Age, race, marital status, education, smoking status, BMI at baseline, alcohol use, total caloric intake, comorbidities score, total physical activity.
Dunstan et al., 2010 (22)	Prospective cohort study.	8,800 Australian adults (≥25 y at baseline) from the AusDiab study.	284 deaths (including 125 cancer deaths) identified through the Australian National Death Index. Median follow-up 7 y.	Total time spent watching TV or videos in the past 7 d.	No significant association between TV-viewing time and cancer mortality (HR, 1.09; 95% CI, 0.96-1.23 for each hour increase in TV time). TV time was associated with increased risk of all-cause mortality (HR, 1.11; 95% CI, 1.03-1.20 for each hour increase) and cardiovascular mortality (HR, 1.18; 95% CI, 1.03-1.35).	Age, sex, waist circumference, exercise. Models assessing association with categorical TV time additionally adjusted for smoking, education, total energy intake, alcohol intake, diet quality index, hypertension, total plasma cholesterol, HDL-C, serum triglycerides, lipid-lowering medication use, glucose tolerance status.
Katzmarzyk et al., 2009 (27)	Prospective cohort study.	17,013 Canadians ages 18-90 y at baseline.	1,832 deaths (including 547 from cancer) identified through the Canadian Mortality Database. Mean follow-up 12 y.	Predefined categories for time spent sitting during the course of most days of the week.	No association between daily sitting time and cancer mortality (almost all of the time vs almost none of the time; HR, 1.07, 95% CI, 0.72, 1.61). Daily sitting time associated with increased risk of all-cause mortality (HR, 1.54; 95% CI, 1.25-1.91) and cardiovascular deaths (HR, 1.54; 95% CI, 1.09-2.17).	Age, smoking, alcohol consumption, leisure-time physical activity, Physical Activity Readiness Questionnaire.

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Table 1. Studies investigating the associations of sedentary behavior and cancer (Cont'd)

Authors	Design	Sample	Outcome	Measure of sedentary behavior	Results	Adjustment for confounding
Sedentary behavior and health outcomes in cancer survivors						
Lynch et al., 2010 (36)	Cross-sectional study.	111 breast cancer survivors (mean age 69) from NHANES 2003-2006.	Objectively assessed waist circumference and BMI.	Accelerometer-measured sedentary behavior (<100 counts/min).	Sedentary time not associated with waist circumference (β = 2.687; 95% CI, −0.537 to 5.910) or BMI (β = 0.412; 95% CI, −0.811 to 1.636) in fully adjusted models.	Age, ethnicity, total energy intake, moderate- to vigorous-intensity physical activity.
Lynch et al., in press (37)	Cross-sectional study.	103 prostate cancer survivors (mean age 75 y) from NHANES 2003-2006.	Objectively assessed waist circumference.	Accelerometer-measured sedentary behavior (<100 counts/min).	Sedentary time not associated with waist circumference (β = 0.678; 95% CI, −1.389 to 2.745) in the fully adjusted model.	Age, educational attainment, total energy intake, moderate- to vigorous-intensity physical activity.
Wijndaele et al., 2009 (38)	Prospective cohort study.	1,867 colorectal cancer survivors with BMI ≥18.5 kg/m^2 (mean age 65 y).	Change in BMI from baseline to 24 and 36 mo postdiagnosis.	Predefined categories for time spent watching TV on an average day in the past month.	TV ≥5 vs <3 h/d associated with increase in BMI at 24 mo (0.72 kg/m^2; 95% CI, 0.31-1.12; P < 0.001) and 36 mo (0.61 kg/m^2; 95% CI, 0.14-1.07; P < 0.01).	Age, sex, educational attainment, marital status, smoking, cancer site, cancer stage, mode of treatment, comorbidities, physical activity.

Abbreviations: CPS-II, Cancer Prevention Study II; NIH-AARP, National Institutes of Health - American Association of Retired Persons; EPIC, European Prospective Investigation of Cancer; HR, hazard ratio; AusDiab, Australian Diabetes, Obesity and Lifestyle Study; HDL-C, high density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey.

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predetermined occupational activity categories in which "mostly sitting" was an option for participants to select (21, 29); one of these studies also included an item on usual leisure-time activity, with response categories that included "sedentary" ("reading," "watching TV"; ref. 21). One study administered two items asking for time spent watching television on weekdays and weekends separately (28), and one study asked five questions relating to different occupational and leisure-time sedentary activities (35). Finally, one study asked participants about occupational activity across the lifespan. Participants assigned an intensity level to the main tasks of each job, and occupational sedentary time was derived from all time reported from work activities coded as "mainly sitting down" (24).

The reference recall periods for the sedentary behavior measures also varied. Two studies directed participants to report their usual behavior (26, 28), five studies referred to average daily time over the past year (21, 23, 25, 30, 31), two studies asked participants to recall average daily time 5 years prior (33, 35), and one study examined lifetime occupational sitting (24).

To address the question of how sedentary behavior was associated with colorectal cancer, the randomized controlled trial data were analyzed as for a prospective cohort. Cox proportional hazards models estimated the RRs; models were adjusted for intervention group and age, body mass index (BMI), smoking (colon cancer), or intervention group and age (rectal cancer). The risk estimates reported by the prospective cohort studies were adjusted for a comprehensive range of potentially confounding variables (23, 25, 26, 29-31). All but one of the prospective studies controlled for physical activity in fully adjusted models (23, 25, 26, 29, 30). There was considerable variation in adjustment for confounding across the case-control studies: The breast and ovarian cancer case-control studies adjusted for a range of sociodemographic, anthropometric, and reproductive factors, as well as physical activity (28, 35), whereas the colorectal cancer case-control study adjusted models for education and total energy intake only (33). The endometrial cancer case-control study estimated risk ratios for age- and total physical activity–adjusted models; however, the fully adjusted models from this study did not include physical activity (24).

Sedentary behavior and cancer mortality. Four prospective cohort studies examined the association between sedentary behavior and overall cancer mortality. One study observed a statistically significant increased risk (32), two studies observed nonsignificant risk increases (22, 34), and the fourth study presented null results (27). Each study sample was composed of adults who were representative of their broader community. The survival analysis conducted using the Cancer Prevention Study II Nutrition Cohort examined the contribution of leisure-time sitting to risk of cancer death separately for men and women. There were 3,881 cancer deaths in men and 3,108 in women over the 14-year follow-up (32). The modest size of the other cohorts meant cancer deaths recorded within the follow-up period ranged between 570 (34) and 125 (22), making many site-specific cancer mortality analyses unfeasible.

Sedentary behavior was assessed using fairly crude self-report measures. Television viewing on weekdays and weekends was assessed over the past 7 days (22) or the past year (34); other studies asked participants to report the total amount of time spent sitting (27) or the amount of time spent sitting outside of work (32) on a usual day, using predetermined categories. Three studies adjusted their hazard ratio estimates for a range of sociodemographic, health behavior (including physical activity), and cardiometabolic confounders (22, 32, 34). The mortality analyses of the fourth study were adjusted for age, smoking status, alcohol consumption, leisure-time physical activity, and the Physical Activity Readiness Questionnaire, which asks participants to report whether they have a range of exercise contraindications such as heart conditions (27).

Sedentary behavior in cancer survivors. Three studies, one prospective (38) and two cross-sectional (36, 37), examined associations of sedentary behavior with adiposity in cancer survivors. A cross-sectional study of breast cancer survivors reported a positive association for accelerometer-assessed sedentary time with waist circumference ($\beta = -9.81$; 95% CI, −15.84 to −3.78) and BMI ($\beta = -3.58$; 95% CI: −6.69 to −0.46) in models adjusted for age, ethnicity, and total energy intake. However, these associations were attenuated by further adjustment for moderate- to vigorous-intensity physical activity (36). A cross-sectional study of sedentary time and adiposity in prostate cancer survivors found no discernible association (37). In a prospective study of colorectal cancer survivors, recall of average daily television viewing time over the past month (≥5 versus <3 hours per day) was positively associated with a mean increase in BMI of 0.71 kg/m^2 over ~18 months (38).

The cross-sectional studies of sedentary behavior in cancer survivors included 111 and 103 self-reported breast and prostate cancer survivors, respectively, from the National Health and Nutrition Examination Survey 2003 to 2004 and 2005 to 2006 (36, 37). The prospective study examined the relationship between sedentary behavior and weight gain in a large cohort of colorectal cancer survivors recruited through a population-based registry.

Sedentary behavior was assessed objectively, by accelerometer, in both of the cross-sectional studies. A cutoff of <100 cpm was used categorize sedentary time from light-intensity physical activity (36, 37). In the prospective study, participants provided an estimate of their television viewing time, on an average day, over the past month (38). The modest sample sizes of the cross-sectional studies restricted the number of covariates adjusted for in the models. The fully adjusted breast cancer models were controlled for age, ethnicity, total energy intake, and physical activity (36); the prostate cancer model was adjusted for age, educational attainment, total energy intake, and physical activity (37). The prospective study was able to adjust for a range of clinically important

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confounders, including physical activity; however, energy intake was not assessed and accounted for (38).

Biological pathways

An overview of hypothesized mechanisms by which sedentary behavior may contribute to the development and progression of cancer is illustrated in Fig. 2. This figure suggests that adiposity accumulated through sedentary behavior is likely an independent contributor to cancer and a mediating variable on the other pathways.

Adiposity. Adiposity may facilitate carcinogenesis through a number of pathways, including increased levels of sex hormones, insulin resistance, chronic inflammation, and altered secretion of adipokines (111, 112). There is convincing evidence that excess body weight increases cancer risk (particularly colon, postmenopausal breast, endometrial, kidney, and esophageal) and cancer-related mortality (3, 113-115).

Sixty-two studies that met review criteria addressed the association between sedentary behavior and adiposity (see Table 2). The randomized controlled trial assessed the effect of a 3-week television-viewing-reduction intervention. The overweight adult participants were assigned to either a 50% reduction of their usual television viewing (intervention) or usual television viewing (control). Participants in the intervention group experienced a greater reduction in BMI than participants in the control group; however, the between-group difference was not statistically significant (98). Five of the 10 prospective cohort studies found statistically significant, positive associations between sedentary behavior and measures of adiposity or weight gain (15, 89-92). The risk estimates for highest versus lowest categories of sedentary behavior ranged from a RR of 1.94 (95% CI, 1.51-2.49) for obesity (BMI >30 kg/m^2) at follow-up (15) to an OR of 1.18 (95% CI, 1.12-1.24) for weight gain of >5% from baseline to follow-up (92). One prospective study, which had only measured sedentary behavior at follow-up, found a positive association (OR, 1.49; 95% CI, 1.21-1.83) between weight gain (from baseline to follow-up) and higher levels of sedentary behavior at follow-up (93). A second prospective study found that baseline sedentary behavior (assessed by individually calibrated heart rate monitoring) did not predict fat mass, BMI, or waist circumference

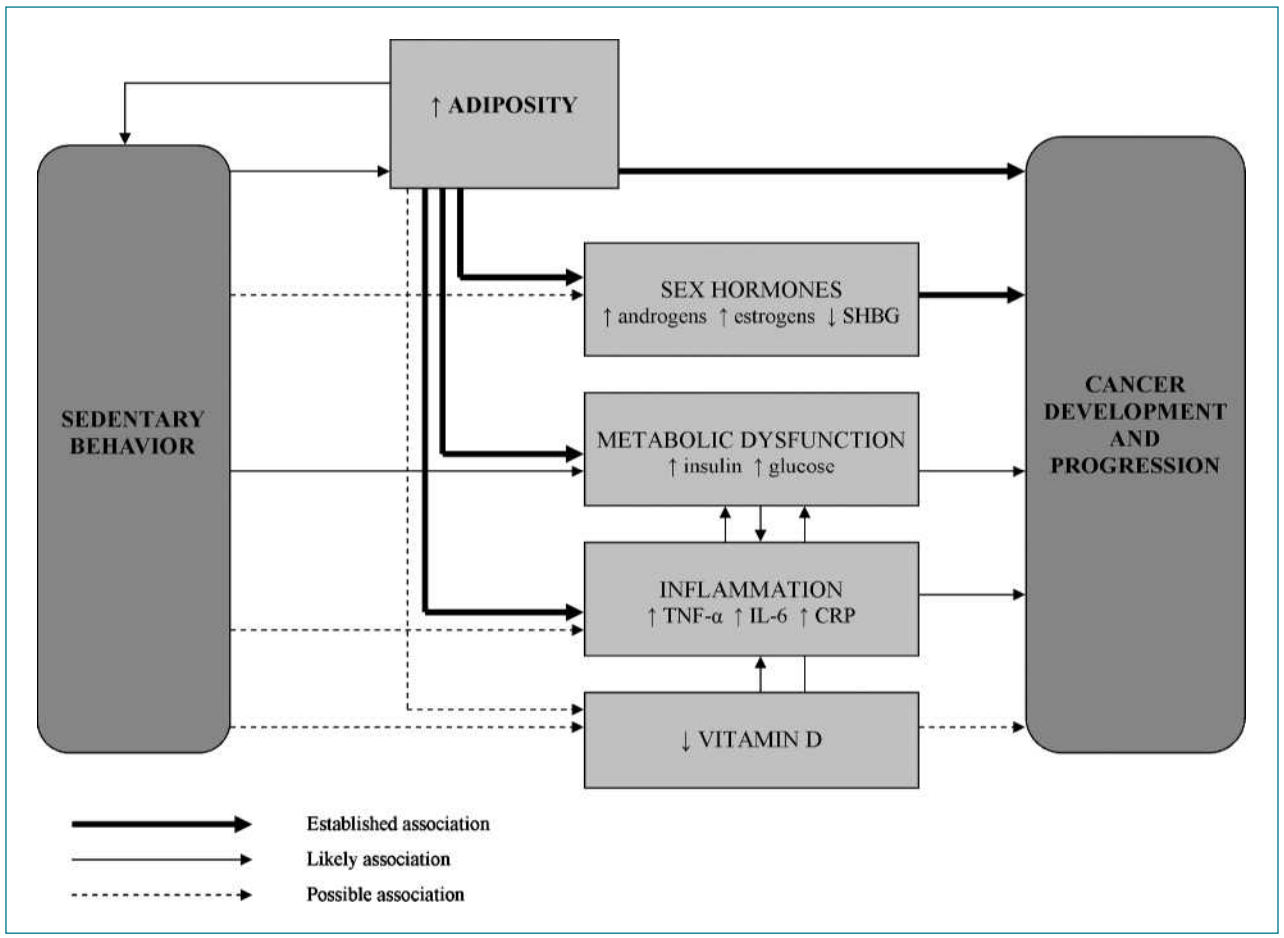

Figure 2. Biological model of hypothesized pathways from sedentary behavior to cancer. TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; CRP, C-reactive protein.

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Table 2. Results from epidemiologic studies of proposed biological pathways and sedentary behavior

Proposed biological pathway	Type of study design, association between sedentary behavior and pathway, and number of studies*			
	Cross-sectional studies		Prospective studies	
	+	Nonsignificant	+	Nonsignificant
Adiposity	42 (12; 16; 39-79)	9 (61; 80-88)	6 (15; 89-93)	5 (94-98)
Sex hormones		1 (109)		
Metabolic dysfunction	4 (52; 101; 105; 108)	3 (17; 84; 109)	1 (14)	3 (89; 106; 107)
Inflammation			1 (107)	
Vitamin D	1 (110)			

NOTE: +, Statistically significant, positive (deleterious) association between sedentary behavior and biological pathway; nonsignificant, no statistically significant association between sedentary behavior and biological pathway. None of the studies reviewed reported statistically significant negative associations between sedentary behavior and biological pathway.

*Some studies assessed multiple biomarkers and therefore may have multiple associations indicated; some studies produced more than one publication.

at follow-up; however, baseline measures of adiposity significantly and independently predicted the amount of sedentary time at follow-up (94).

There were 51 cross-sectional studies of sedentary behavior and adiposity or related measures (e.g., BMI or waist circumference), of which 42 found statistically significant associations (12, 16, 39-79), and one further study showed a borderline positive association (80). Among the studies where the outcome was defined as BMI $\geq$25 kg/m^2, the ORs for highest versus lowest categories of sedentary behavior ranged from 1.27 (95% CI, 0.23-6.95) to 2.27 (95% CI, 1.55-3.32; refs. 41, 46, 51, 54, 57, 60, 62, 64, 66, 68, 71, 74, 80, 85, 86, 116). Where BMI $\geq$30 kg/m^2 was the study outcome, ORs for highest versus lowest sedentary behavior ranged from 1.20 (95% CI, 1.00-1.40) to 2.52 (95% CI, 1.81-3.51; refs. 48, 50, 56, 60, 70, 73, 77, 78).

Sex hormones. Exposure to biologically available sex hormones is a risk factor for hormone-related cancers, particularly breast, endometrial, and prostate cancers (117, 118). Levels of sex hormone binding globulin (SHBG) may also affect cancer risk; SHBG binds to sex hormones, rendering them biologically inactive (111, 117). Adiposity can amplify the association between sex hormones and cancer risk. In postmenopausal women, the main source of circulating estrogen is from androgen aromatization, which commonly occurs in adipose tissue (117, 118). Further, visceral adipose tissue is thought to be important in the production of adipocytokines, which influence estrogen biosynthesis (119).

Only one study identified by this review assessed the relationships between sedentary behavior and sex hormones (Table 2). Tworoger and colleagues examined cross-sectional associations of sitting time (at work and home) with sex hormone levels (estradiol, free estradiol, estrone, estrone sulfate, testosterone, free testosterone, androstenedione, DHEA, DHEA sulfate, progesterone, SHBG) in 565 premenopausal women. No statistically significant associations were found, although a nonsignificant trend was observed for the association between sitting and follicular estrone (109).

Metabolic dysfunction. Insulin resistance describes diminished ability to maintain glucose homeostasis, and is often characterized by hyperinsulinemia and hyperglycemia. Insulin resistance may promote the development of cancer by several pathways. Neoplastic cells use glucose for proliferation; therefore, hyperglycemia may promote carcinogenesis by providing an amiable environment for tumor growth (120). High insulin levels increase bioavailable insulin-like growth factor-I, which is involved in cell differentiation, proliferation, and apoptosis (121). Insulin can also indirectly increase bioavailability of estrogen and androgen (122). A recent meta-analysis showed increased risks of colorectal and pancreatic cancers associated with elevated levels of circulating insulin and blood glucose (123). Mixed results were found for breast and endometrial cancer; however, recently published, large prospective studies have reported positive associations between insulin and breast and endometrial cancer risk (124, 125).

Four prospective and seven cross-sectional studies of sedentary behavior and biomarkers of metabolic dysfunction (glucose, insulin, insulin resistance, C-peptide, insulin-like growth factor-I or insulin-like growth factor binding protein-3, or a combination of these measures) were identified by this review (Table 2). A statistically significant association was observed in one of the four prospective studies. Baseline sedentary behavior (defined by heart rate observations below an individually predetermined threshold) was independently associated with fasting plasma insulin at follow-up in a sample of 376 middle-aged adults (β = 0.004; 95% CI, 0.009-0.006; ref. 14). The other prospective studies examined sedentary behavior and insulin (106, 107) or fasting plasma

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glucose levels (89), and no significant associations were observed. Four of the seven cross-sectional studies found statistically significant, positive associations between sedentary behavior and metabolic biomarkers. Positive associations were observed with insulin (52), insulin resistance (101, 105), and 2-hour glucose (108), but not with fasting plasma glucose (17, 84, 108) or insulin-like growth factors (109).

Inflammation. Chronic inflammation is acknowledged as a risk factor for numerous cancers (111, 118). Increased levels of pro-inflammatory factors, namely adipokines (including tumor-necrosis factor-α, interleukin-6, leptin) and C-reactive protein, and decreased levels of anti-inflammatory factors (adiponectin) may indicate a higher cancer risk. Obesity is considered a low-grade, systemic inflammatory state, and as such levels of inflammatory markers are elevated among individuals who are obese (111).

In the only study of sedentary behavior and biomarkers of inflammation, Fung and colleagues assessed the prospective association between television viewing time and leptin in 468 men. A significant, positive association between average television viewing hours (four assessments from 1998 to 1994) and leptin was observed: β = 0.8 (SEM 0.4), $P < 0.05$. This relationship was independent of age and a range of lifestyle factors, including physical activity and BMI (107).

Vitamin D. Vitamin D is acquired primarily through UV irradiation, and to a lesser extent from dietary sources. It is metabolized in the liver to 25-hydroxyvitamin D [25(OH)D], which is the form considered the best indicator of an individual's vitamin D status (126). 25(OH)D is further metabolized to the biologically active form of vitamin D, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], in the kidneys and other target tissues (126, 127). 1,25$(OH)_2$D is an active secosteroid that has different effects on various target tissues. In the tumor microenvironment, 1,25$(OH)_2$D plays an important role in the regulation of differentiation, proliferation, and apoptosis (127, 128). Studies have shown adiposity to be associated with lower levels of 25(OH)D, likely because vitamin D is fat soluble and is readily stored in adipose tissue (129, 130). Levels of vitamin D have been shown to be more than 50% lower in obese individuals than in nonobese individuals exposed to the same dose of UV-B radiation (130). It has also been hypothesized that obese individuals may receive less sun exposure due to limited mobility or preference for indoor, sedentary leisure pursuits (129).

Ecologic studies have linked residence at higher latitudes, and hence lower levels of sun exposure, with higher cancer incidence and mortality (126, 131). A number of prospective cohort studies have examined the association between vitamin D and cancer outcomes in more detail. 25(OH)D has been associated with increased colorectal (132, 133), colon (134), and pancreatic (133) cancer risk. Additionally, exogenous vitamin D intake has been associated with reduced premenopausal (135) and postmenopausal breast cancer risk (136), and reduced pancreatic cancer risk (137).

There are limited data on the association between sedentary behavior and vitamin D status. A cross-sectional analysis in the British Birth Cohort showed a significant, sex- and season-adjusted difference in adult participants' 25(OH)D levels across television-viewing time categories (110). Vitamin D deficiency (25[OH]D <15 ng/mL) has also been associated with higher volumes of television-viewing time among children and adolescents in the National Health and Nutrition Survey 2001 to 2002 and 2003 to 2004 (138).

Discussion

Sedentary behavior research is a newly emerging field, particularly with regard to understanding its role in cancer pathogenesis and progression. Insufficient evidence has accumulated to draw strong conclusions about associations between sedentary behavior and cancer. However, broadly, the epidemiologic research to date has linked sedentary behavior with colorectal, endometrial, ovarian, and prostate cancer development; cancer mortality in women; and with weight gain in colorectal cancer survivors. These statistically significant associations were predominantly shown in large, population-based samples, and models were well adjusted for possible confounding variables.

The sedentary behavior exposure measures used in the studies identified were heterogeneous. They ranged from a single item assessing usual daily hours of nonoccupational sitting time (32) to a structured questionnaire to assess sedentary behavior across a range of occupational and leisure-time activities (35). The test-retest reliability of sedentary behavior measures tends to be strong; items pertaining to television viewing or nonoccupational sitting time generally have an intraclass correlation coefficient of 0.75 or higher (9). However, few sedentary behavior measures have been validated, and those that have demonstrate low to moderate correlation (9). Only two of the studies included in the review of sedentary behavior and cancer reported objectively assessed sedentary time (36, 37).

The second part of this review considered potential biological pathways that may at least partially explain the observed associations between sedentary behavior and cancer. Of the possible pathways that may mediate an association between sedentary behavior and cancer, the most consistent evidence has accumulated for adiposity. Sedentary behavior and adiposity are consistently associated in cross-sectional studies; results from prospective studies, however, suggest that the relationship may be bidirectional. Modest evidence has also accumulated linking sedentary behavior with biomarkers of metabolic function, with stronger associations again emerging from cross-sectional studies. Although biological plausibility exists, there is insufficient epidemiologic evidence to draw any conclusions about the associations of sedentary

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behavior with sex hormones, inflammation, and vitamin D. The potential biological pathways considered by this review may also underlie the relationship between physical activity and cancer (111, 118, 139). However, it is possible that sedentary behavior may also exert its influence through other mechanisms, as it initiates some unique cellular processes that are qualitatively different from exercise responses. Hamilton and colleagues have shown in studies of laboratory rats that sedentary behavior has a differentially greater effect on lipoprotein lipase regulation than exercise training (4, 140). Additionally, Hamilton's group identified genes in skeletal muscle whose expression is most sensitive to inactivity. They hypothesized that these genes may be involved in the initial muscle adaptations to repeated episodes of sedentary behavior, and in the etiology of diseases for which sedentary behavior is a risk factor (141).

Sedentary behavior is ubiquitous in contemporary society. The high prevalence of obesity and other "lifestyle diseases" is frequently linked to technological advances that have automated many domestic and occupational tasks, which in the past would have required significant physical exertion (20, 142). Public health efforts have focused on increasing participation in discretionary (usually leisure-time) physical activity as a key strategy for combating chronic disease. Based on accumulating evidence of the detrimental health effects of sedentary behavior, it has been suggested that future public health guidelines for physical activity will also incorporate recommendations to reduce prolonged sitting time (5). Currently, cancer prevention guidelines recommend participation in regular physical activity, although there is uncertainty regarding optimal dose and timing of physical activity for cancer prevention (143). Physical activity is also recommended for cancer survivors, and there is accumulating evidence on its quality, and quantity, of life benefits (144). To determine whether reducing sedentary behavior concurrently with appropriate increases in physical activity may be a viable new cancer control strategy, additional research is required.

Recommendations

Research on physical activity and health frequently characterizes individuals who report no participation in purposive physical activity as "sedentary" (5). This is evidenced by the huge disparity between the number of articles retrieved by the search terms "sedentary behavior" and "cancer" and the number of articles included in this review. This definition, however, aggregates truly sedentary behaviors (prolonged sitting or lying down) with light-intensity activities that are difficult to measure by questionnaire. Light-intensity physical activities, which include routine domestic or occupational tasks, are the predominant determinant of variability in adults' total daily energy expenditure (145). Hence, sedentary behavior should be considered as a distinct construct, independent of physical activity. As such, the term "sedentary behavior" should be applied to activities of low energy expenditure characterized by prolonged sitting. "Physical inactivity" best describes the absence of health-enhancing physical activity.

Given that research on sedentary behavior and cancer is in its early stages, there are opportunities to improve methods of sedentary behavior measurement before further research efforts are expended. Objective measurement of sedentary behavior, by accelerometers or heart rate monitors, provides many advantages; however, these methods cannot differentiate between different contexts or types of sedentary behaviors. Newer techniques for measuring sedentary behavior include combined sensing (a combination of motion and heart rate monitoring; ref. 146) and triaxial raw data accelerometers that record acceleration data in three (vertical, mediolateral, and anterior-posterior) axes. Nevertheless, it is not always practical or affordable to use instruments such as these in large epidemiologic studies. Hence, the development and validation of comprehensive self-report measures of sedentary behavior is required (9, 147).

Additional observational studies are needed to quantify the associations of sedentary behavior with cancer risk and outcomes (particularly survival), and also with biomarkers that may be operative in the pathogenesis and progression of cancer. Future studies would benefit from the explicit assessment and control of confounding factors, particularly measures of adiposity, moderate- to vigorous-intensity physical activity, and energy intake. The possible interactive effect of sedentary behavior and physical activity is also an important question that has not been adequately addressed by studies to date. The deleterious effect of sedentary behavior has been shown even among individuals engaging in high levels of physical activity in studies examining all-cause mortality (32) and cardiometabolic biomarkers (13). The question of how the detrimental effects of sedentary behavior are mediated by level of physical activity needs also to be addressed in relation to cancer risk. Prospective cohort studies are required to investigate cancer sites for which there are plausible biological pathways between sedentary behavior and cancer, such as postmenopausal breast and lung cancer. Insulin resistance, insulin-like growth factors, adipokines, and vitamin D are mechanisms that might underlie such associations (18).

Observational studies are also needed to examine associations with biomarkers; how sedentary behavior may be associated with mechanisms operative in cancer pathogenesis have only begun to be explored, and there are numerous avenues for inquiry to be pursued. Findings from experimental studies may offer insight into biological pathways to be explored in epidemiologic studies. For example, a recent trial found that 2 weeks of bed rest with eucaloric diet activated a proinflammatory response, as indicated by increases in plasma C-reactive protein and interleukin-6, and decreases in interleukin-10 (148). In another laboratory trial, lifelong sedentary behavior in mice led to accelerated muscle mitochondrial dysfunction and increased levels of mitochondrial oxidative damage (149).

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A decline in mitochondrial function may contribute to neoplastic transformation and metastasis (150). Whereas the results of bed-rest studies and experiments in laboratory mice may not extrapolate to free-living humans, these findings suggest that the associations of sedentary behavior with markers of inflammation and mitochondrial function warrant investigation.

Future research directions suggested for sedentary behavior and cancer risk are also applicable to studies of cancer survivors. Issues of cancer survivorship are becoming increasingly important as worldwide trends in aging continue and diagnostic and treatment techniques improve. Currently, there are an estimated 12 million cancer survivors in the United States (144). Cancer survival is associated with significant decrements in health status and an increased risk of death from noncancer causes (151). The burden of survival includes an increased risk of morbidity and premature mortality related to comorbid chronic diseases, such as type 2 diabetes and cardiovascular disease (152, 153). The role of sedentary behavior in cancer survival is largely unexplored; however, it could plausibly contribute to the progression of cancer and the development of comorbid chronic disease.

Understanding the sociodemographic correlates of sedentary behavior in the broader population at risk for developing cancer, and in specific populations of cancer survivors, is another research priority. The contextual determinants, or behavior settings (154, 155), in which these different populations are most likely to engage in sedentary behavior also need to be determined. Classifying the characteristics of the most sedentary individuals and the contexts in which sedentary behavior is most likely to occur is useful for identifying prime candidates for intervention (156).

Should sedentary behavior be consistently associated with cancer risk and health outcomes in cancer survivors, intervention trials will be necessary to establish the efficacy of reducing sedentary behavior to reduce cancer incidence and cancer progression/recurrence. Such trials, ideally as randomized controlled trials, will also be needed to compare the relative merits of various types of interventions that reduce or break up extended periods of sedentary behavior.

Finally, future research will need to extend beyond the randomized, controlled trial design to address translation into health promotion programs that aim to change knowledge, beliefs, and attitudes toward sedentary behavior. Well-designed primary prevention programs should be guided by relevant frameworks; thus, there is a need for assessment of how comprehensive models of health behavior change can be applied to the diffusion of sedentary behavior interventions (155). Decreasing sedentary behavior might also be approached through changes to the social and physical environment (4, 5).

Conclusions

The first studies of sedentary behavior and cancer have shown that prolonged sitting is independently associated with colorectal, endometrial, ovarian, and prostate cancer risk; cancer mortality in women; and with weight gain in colorectal cancer survivors. Future research in this area will establish whether reducing sedentary behavior is a novel and viable cancer control strategy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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