REVIEW

Physical Activity in the Prevention of Cancer

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Abstract

Objective: The purpose of this paper is to update epidemiological research on relations between physical activity and cancer risk, including physical activity measurement and potential mechanisms of prevention of cancer. Design: Review of recent systematic reviews, meta-analyses and studies on the topic that have been published in the recent literature. Results: Convincing epidemiological evidence exists that physical activity reduces colon and breast cancers. The evidence is weaker for prostate (classified as probable), lung and endometrial cancers (classified as possible), and insufficient for cancers at all other sites. Hypothesized biological mechanisms for the physical activity – cancer association include changes in hormone level, reduced percentage of body fat, enhancement of the immune system, and alteration in free radical damage by scavenger systems. The available data indicate that 30-60 minutes per day of moderate-to vigorous physical activity is needed to be protective against breast and colon cancers. Conclusion: A greater understanding of the biological mechanisms operating in the physical activity – cancer relation, complete measurements of physical activity through a subject's life, assessment of all potential confounders and association modifiers are needed to confirm a protective role of physical activity in cancer development and allow specific exercise prescriptions for prevention in particular cancer sites.

Key Words: Cancer - physical activity - prevention

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Introduction

Cancer remains a major public health problem in developed countries due to industrialization, changes in lifestyles, population growth and increase in the proportion of elderly persons, despite advances for diagnosis and treatment. It was reported that approximately over 10 million new cases of cancer (5.3 million men and 4.7 million women) occurred in 2000 and over 6 million people died from cancer in the world (Parkin, et al., 2001). According to the National Center for Health Statistics there will be approximately 1,334,000 new cases of cancer in 2003 and about 556,500 deaths due to the disease in the United States (Jemal et al., 2003). The most commonly estimated new cases of cancers among men were: prostate, lung and bronchus, colon, colorectal, and rectal cancers (32.7%, 13.6%, and 10.8%, respectively), and for women – breast (32.1%), lung and bronchus (12.2%), and colorectal (12.9%) (Kelsey & Gammon, 1991). Population based cancer registry is the source of all cancer cases occurring in a particular region of the world.

The first finding that physical activity may be preventive against cancer disease was dated since 1922. Two groups of investigators Cherry (1922), and Sivertsen & Dahlstrom (1922), reported independently, that the mortality rates on account of cancer in Australia, England and the United States among men declined with increased occupational physical activity. Since this first report that physical activity may influence cancer risk, more than 190 epidemiological studies have examined the relation between physical activity and different site-specific cancers. This association has been reviewed several times (e.g. Friedenreich & Thune, 2001; Hardman, 2001; Thune & Furberg, 2001; Friedenreich & Orenstein, 2002; Lee, 2003; McTiernan 2003; Willer 2003; Quadrilatero & Hoffman-Goetz 2003; Lagerros et al., 2004; Kruk 2005). A large number of evidence shows that 80-90% of human cancer may be attributable to environmental and lifestyle factors (dietary habits, physical activity, alcohol consumption and tobacco use (McPherson et al., 1994; Brewster & Helzlsouer, 2001; Kushi & Giovannucci, 2002; Okasha et al., 2003, Murthy & Mathew 2004). However, the type, intensity, amount of physical activity needed to be protective is unknown (Mc Tiernan, 2003).

The purpose of the present report is to discuss the main recently published data concerning an association between physical activity and cancer risk including: (a) the actual

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state of knowledge; (b) appropriate measurement of physical activity; and (c) potential biological mechanisms. This paper is not intended to be a comprehensive review of data from investigators on this subject, but it updates the evidence since recently published reviews. Public health strategy to stimulate people to be physically active as a response on the global burden of civilization diseases attributable to physical inactivity, among them, cancer requires of constant updating of the evidences on this topic.

Actual State of Knowledge on the Association between Physical Activity and Cancer

The scientific evidence for a protective role of physical activity as a mean for the primary prevention of cancer is accumulating rapidly. There is now strong evidence that physical activity can reduce breast and colon cancers. Life style factors (physical inactivity, obesity, alcohol consumption, smoking and exposure to ionising radiation), dietary factors (red meat and animal fat, sugar, low consumption of vegetables, fruits), genetic family history, hormonal and reproductive factors, biological factors (e.g., virus infections, hepatitis B or C virus, human T-cell leukaemia virus, helicobacter pylori), advancing age, and environmental or occupational agents (e.g., asbestos, polychlorinated biphenyls, chromium, beryllium, nickel) are the causal factors for cancer. Among the above mentioned potential risk factors the physical activity, age at first menstrual period, reproduction, tobacco use, alcohol consumption, dietary intake, can be modified through lifestyle-behaviour change, and their modification may result in a decreased incidence of the cancer diseases (Doll & Peto, 1981; McPherson et al., 2000; Hulka & Moorman, 2001; Liehr & Jones, 2001;Thune & Furberg, 2001; Collaborative Group on Hormonal Factor in Breast Cancer 2001; Hamajima et al., 2002; Key et al., 2002; Kushi & Giovannucci, 2002; Willer, 2003; Bauman 2004; Murthy &Mathew, 2004; Stein & Colditz, 2004; Gotay, 2005). It is worth of emphasis that the importance of behavioral factors in cancer etiology was demonstrated already in 1981, and Doll and Peto (1981) were the first to report on relation between the cancer incidence and lifestyle.

The relation between a potential risk factor (e.g., smoking) and cancer is most frequently explored in the epidemiological literature by examining relative risk (RR) or odds ratio (OR). Relative risk indicates how many times more or less is likely that breast cancer occurs in the exposed group (i.e., smokers) compared with the unexposed group (nonsmokers) (Schlesselman & Stolley, 1982). If RR = 1 then considered factor is not associated with an increased risk of the disease. For RR > 1, a positive association occurs; the smokers have a higher risk of a cancer than it is in nonsmokers; for RR < 1 the negative association (smokers have a lower risk of a cancer than nonsmokers) is observed. Another measure of the association between a factor and breast cancer is the odds ratio (OR); OR is very close related to the RR. The OR can be calculated from either a cohort or a case-control study, whereas the RR can be exactly determined from the cohort study. Determination of the RR from a case-control study requires of the OR approximation (Schlesselman & Stolley, 1982). In order to estimate the range of factor influence on cancer, the risks are reported with 95% confidence intervals (CI). For example, RR or OR = 2.0 means that the risk of cancer for smokers compared to nonsmokers is somewhere between similar risk (OR = 1.0) to twice the risk among smokers compared to nonsmokers (OR = 2.0).

The scientific evidence for the relationship between physical activity and cancer risk is classified according to the definitions developed by the World Cancer Research Fund/American Institute for Cancer Research report (1997) on food, nutrition and the prevention of cancer and further evaluated in the IARC handbook (IARC, 2002). In the report the following four categories of the relation were defined and used: “convincing”, “probable”, “possible” and “insufficient”. “Convincing” evidence means that evidence is conclusive and the term needs fulfilment of the following conditions: consistency of evidence for a risk reduction with increased levels of physical activity results from at least 20 studies including prospective designs; the studies were conducted in different populations and were controlled for possible risk factors; the exposure factors preceded the cancer disease occurrence; a dose-response relation across increasing activity levels is observed; the relation is biologically possible (Friedenreich, 2001a). “Probable” evidence indicates that the data from epidemiological studies are less consistent, the number of studies supporting the relation is not sufficiency to make a definitive judgement but mechanistic and laboratory data are strongly supportive. “Possible” evidence means that a causal relation may exist. In this case the epidemiological studies are mainly supportive but they are limited in quantity, quality or consistency, and mechanistic and laboratory data may or may not be supportive. “Insuficient” term exists when the evidence is suggestive but that is insufficient to make definitive judgement. In case of this evidence only few studies are consistent and they can only suggest a possible association.

Data on relation between physical activity and risk of cancer comes from case-control and cohort studies. In case-control studies the level of physical activity is determined on the basis of recall for defined period(s) of time before the cancer diagnosis. Instead, cohort studies enroll healthy participants to evaluate physical activity and other elements of lifestyle, behavior, and environment that are considered to effect later development of cancer (Laporte et al., 1985).

Among cancer prevention epidemiologic studies the best evidence for a protective influence of physical activity exists for the colon and colorectal cancers. Of total colorectal cancers about 75% belongs to the colon cancers (Jemal et al., 2003). The scientific evidence for an association between the physical activity and these two cancer sites is basically the same and is classified as convincing (Friedenreich & Orenstein, 2002). Lower risk of colon cancer has been observed in different countries among male and female participants of epidemiologic studies who reported moderate to vigorous leisure-time, sports and recreational activities and/or work at occupations requiring high degrees of physical exertion. The significance of physical activity in the colon prevention has been shown as an independent predictor of this site cancer and through its impact on the odds ratios associated with other risk factors, for an example, with a diet, in particular, with an intake of vegetables and fruits (Slattery & Potter, 2002). The authors had surveyed 1993 cases and 2410 controls and found that the relative importance of diet in the colon prevention was dependent on the level of physical activity. In participants of high physical activity levels the risk of colon cancer associated with high vegetable intake was 0.9 (95% CI: 0.6 – 1.3), whereas the risk associated with high vegetable intake in more sedentary participants was found to be 0.6 (95% CI: 0.5 – 0.9). To date, at least 51 studies on the relation between physical activity and colon / colorectal cancers have been conducted in many countries in Europe, America, Asia (reviewed in Colditz et al., 1997; Friedenreich, 2001a; Hardman, 2001; Thune & Furberg 2001; Friedenreich & Orenstein, 2002; Lee, 2003; Slattery, 2004). The majority studies (about 80%) showed a reduction in cancer risk among the most physically active persons. The magnitude of decreased risk experienced by physically active individuals has ranged from 0.30 to 0.80, with an average reduction of 40 – 50 % (Friedenreich & Orenstein, 2002). Higher activity has been generally related to reduced risk of colon cancer for both recreational and occupational activities, despite more or less detailed assessment of physical activity and different populations. Of the 51 studies conducted on colon and colorectal cancer 29 studies tested for a dose-response relation and 25 of them reported a significant trend of declining risk with increasingly higher levels of physical activity.

Inconsistent associations are observed for rectal cancer and physical activity. Only 20% of all epidemiologic evidence on the relation found an association (Tune & Furberg, 2001). However, a recent population based case-control study by Slattery et al. (2003), (952 cases and 1,205 controls) in the US found that vigorous physical activity was associated with almost 40% reduction of rectal cancer in both men and women (OR = 0.60, 95% CI: 0.44 – 0.81) and OR = 0.59, 95% CI: 0.40 – 0.86, respectively). The authors also observed a reduced risk of rectal cancer among participants who were classified as moderate active.

To date, at least 64 studies contributed information on the relation between physical activity and breast cancer (reviewed, e.g., in Friedenreich & Rohan, 1995; Gammon et al., 1998; Latikka et al., 1998; Thune & Furberg, 2001; Friedenreich & Orenstein, 2002; Kruk, 2002; Lee, 2003; McTiernan, 2003; Mona et al., 2003; Lagerros et al., 2004; Kruk, 2005). The majority of studies (about 70%) have shown that women who were most active in their occupational and / or recreational activities have a lower incidence of breast cancer than their sedentary counterparts. The evidence for the relation between physical activity and breast cancer is classified as convincing (IARC 2002). This is due to the fact that at least 20 studies conducted worldwide found substantial reduction in the risk among active compared with sedentary subjects. The reported reduction in the risk ranged from 10% to 80%, and was on average 30-40%. The magnitude of risk reduction is found to be somewhat larger among postmenopausal women than that seen in premenopausal women (Friedenreich, 2004a).

Also, the recent hospital based case-control study (2,376 cases, 18,977 controls) conducted in Japan by Hirose and colleaques (2003) provides a quantitative estimate on the relation between physical activity and breast cancer. The authors found a 19% risk reduction among women who exercised reguraly at least twice a week (OR = 0,81, 95% CI: 0.69 – 0.94) irrespective of menopausal status. A particularly strong protective effect of physical activity (43%) was seen among premenopausal women (OR = 0.57, 95% CI: 0.28 – 1.15) for those women whose BMI was 25 or higher. In turn, a 29% risk reduction was found only among those postmenopausal women whose BMI was low (<25). Likewise, a higher reduction in breast cancer risk among premenopausal women was reported by John et al., (2003). The authors assessed lifetime exercise histories for a study of 403 premenopausal cases and 483 controls and 847 postmenopausal cases and 1,065 controls in Latinas, African Americans, and whites, aged 35 – 79 years. They observed reduced breast cancer among women with the highest versus lowest tertile of average lifetime activity (OR = 0.74, 95% CI: 0.52 – 1.05 for premenopausal and OR = 0.81, 95% CI: 0.64 – 1.02, for postmenopausal) in the three racial / ethnic groups.

A dose – response relation over different levels of physical activity was examined in approximately 50% of the studies and about 60% of them found a significant trend of declining breast cancer risk with increased physical activity (Dirx et al., 2001; Drake, 2001; Lee, 2003). In the literature on this relation, there are also a small number of studies which show no association (see, eg., Chen et al., 1997: Lee et al., 2001a; Moradi et al., 2002) or found an association limited only to certain subgroups of subjects (e.g., for premenopausal women having BMI≥30 kg/m_ (Colditz et al., 2003), only for postmenopausal women (Lee et al., 2001b; Patel et al., 2003a; Steindorth et al., 2003) or among women without a family history (Patel et al., 2003b). Some studies reported a higher risk of breast cancer with increased physical activity (see, eg., Pukkala et al., 1993; Dorgan et al., 1994).

Currently, at least 37 studies have examined an association between physical activity and prostate cancer (reviewed in Friedenreich, 2001a; Friedenreich & Thune, 2001; Friedenreich & Orenstein, 2002; Lee, 2003) about a half of which observed a reduction in prostate cancer risk in men who were most physically active. The magnitude of the overall association ranged from a 70% reduction in the risk for the most active compared with the least active subjects to a 287% increased risk (Lee, 2003) with risk reduction averaging 10 – 30% (Friedenreich & Orenstein, 2002). Also, a small number of studies that examined the trend in risk found a decreasing risk associated with increasing levels of physical activity (Friedenreich, 2001a). Likewise, inconsistent evidence comes from a recent case – control study on physical activity and prostate cancer risk conducted in Canada (988 cases, 1063 controls), (Friedenreich et al., 2004b). The investigators observed decreased prostate cancer risks for occupational (OR = 0.90, 95% CI: 6.66 – 1.22) and recreational activities (OR = 0.80, 95% CI: 0.61 – 1.05), increased risk for household physical activity (OR = 1.36, 95% CI: 1.05 – 1.76), and no association for total lifetime physical activity measured in METs per year when, compared the highest and lowest quartiles of activity. When authors examined that relation by intensity of physical activity (men were classified in three categories of activity: < 3 METs-low, moderate 3-6 METs, vigorous > 6 METs) found that men of vigorous activity had 30% decreased prostate cancer risk (OR = 0.70, 95% CI: 0.54 – 0.92) compared to those of low activity. Some studies also observed trends of increased risk with increasing physical activity (Friedenreich, 2001a). The relation between physical activity and prostate cancer risk was classified as probable (IARC, 2002).

Much less evidence exists for the role of physical activity in reducing the risk of lung cancer. With regard to this type of cancer at least 23 studies conducted worldwide have investigated the association of physical activity with the risk of developing lung cancer (for review see Lee, 2003). The majority of studies found decreasing risk with increasing levels of activity: the reduction in risk has ranged from 20 to 60% but a 40% increase in the risk was also reported. The studies were, on the whole, controlled for cigarette smoking (a factor which is considered as a main reason of developing lung cancer). It is worth to add that lung cancer occurs at a very low frequency in these individuals who have never smoked. In addition, a recent study of Kubik and co-workers (2004) conducted among Czech women (419 cases, 1593 controls) demonstrated a reduction in lung cancer risk only among physically active smokers. Also, investigators from Canada (Mao et al., 2003) have reported that risk reduction associated with physical activity was more profound among smokers. They conducted a population – based case – control study of 2,128 cases and 3,106 population controls aged 20 – 76 years, in 1994-1997. They found that individuals in second, third, and fourth quartiles of total recreational physical activity versus lowest active had odds ratios 0.82 (95% CI: 0.68 – 0.98), 076 (95% CI: 0.63 – 0.92), and 0.73 (95% CI: 0.60 – 0.89), respectively, and their finding was statistically significant (p for trend = 0.0008). The lung risk reduction was observed for both men and women classified as moderate to vigorous active. The evidence for a protective role of physical activity in lung cancer is classified as possible.

The next cancer site for which the epidemiological studies have provided possible evidence for decreased risk with increased levels of physical activity is endometrial cancer. As summarized by Friedenreich & Orenstein (2002) of the 13 case-control and linkage studies that have examined the relationship, nine have found lower risk among more active women; reductions found in these studies vary strongly (ranging from 0 to 90%) indicating an average reduction about 30 – 40% for the highest average activity levels compared to the lowest. Of the six studies that examined a dose response effect five have found decreasing risks with increasing activity levels (Levi et al., 1993; Moradi et al., 1998; Terry et al., 1999; Moradi et al., 2000; Litman et al., 2001). These findings are consistent with a recent prospective study of US women by Colbert and co-workers (2003). In this study, involving 23,369 women with 253 endometrial cancer cases, it was found that either total recent physical activity assessed from occupational, leisure – time, household, and sport activities nor vigorous physical activity were not strongly related to the risk of endometrial cancer. However, the researchers observed non-statistically significant 10 – 30% lower relative risk in each of the four higher quintiles compared to the lowest total activity quintile.

Some preliminary evidence that physical activity may also have preventive role against other site – specific cancer (testicular, ovarian, kidney, pancreatic, thyroid and melanoma) exists, however the data are insufficient to make any statement regarding causal association; the evidence remains insufficient.

Definition and Assessment of Physical Activity

Physical activity is defined as any bodily movement produced by skeletal muscles that results in a quantifible expenditure of energy (Caspersen et al., 1985). Physical activity is a complex behaviour and can be categorized in a variety of ways. The simplest categorization includes occupational and leisure-time physical activities. The leisure-time physical activity can be subdivided into the following categories: sports, conditioning exercises, household activity, self-care activity (e.g. bathing, dressing, talking, eating, sitting, standing), child-care activity and others. It is worthwhile mentioning that exercise represents a subset of recreational activity and differs from other types of physical activity in that exercise is structured and planned in order to improve or maintain physical fitness component(s).

There are three primary components of physical activity: intensity (how much energy is expended), duration (refers to the minutes or hours of individual's each activity episode), frequency of muscular contractions (e.g., episodes performed per day, week, or month) (Thompson, 1994). Also a very important feature of physical activity for longer time periods is timing, i.e., period of life (adolescence, adulthood, pre- or postmenopausal periods) in which the individual was engaged (Caspersen et al., 1985).

There are a number of different methods used to measure physical activity (Laporte et al., 1985; Perkins et al., 1995; Ainsworth et al., 1998). These methods can be divided on direct and indirect.

Direct methods measure only energy expenditure but they are intended to be extremely precise. These methods include, for example: observation of movement (e.g. with help of video camera); recording the quantity and/or intensity of movement using motion detectors such as accelerometers, pedometers, electronic and mechanical sensors; measurement of energy expenditure through the release of body heat during physical activity with a help of calorimetry chamber; recording morphologic and cardiorespiratory changes, e.g., the heart rate or blood pressure.

Indirect methods of physical activity determination include physiological measures and surveys. The first measure is based on the fact that changes in the level of high physical activity influence on the cardiorespiratory endurance, ipso facto, cause the frequent consumption of maximum oxygen. The second physiological measure is the doubly labelled water technique – individuals ingest water containing isotopically labelled hydrogen and oxygen atoms. An estimate of energy expenditure by individuals is based on the ratio of unmetabolized water and water incorportated in the energy cycle. Physiological measures represent current health status and are modified by physical activity and comprise metabolic, morphologic and other factors related to the immune response. (For exhaustive survey the reader is referred to the excellent reviews of Laporte et al., 1985 and Ainsworth et al., 1998). Physiological measures are not useful in epidemiological studies because they are expensive for use with large population, in addition inhibit normal physical activity.

Surveys belong to an inexpensive method of physical activity assessment and they are commonly used in epidemiological studies. The survey procedures have the following components: time frame (women are asked to remember their activity); the type and components of physical activity (intensity, frequency, duration); mode of the data collection (personal interview, telephone interview, self-administration, mail sent questionnaire), and a summary index (energy expenditure calculation and physical activity levels determination) (Laporte et al., 1985). The surveys may be short, i.e., consisting of at most four items giving informations on lower or higher level of physical activity in short-time interval, e.g., 24-hours (general); base on questions dealing with physical activity performed in the past week or two weeks (recall), and similar to the recall method, but inquiring physical activity performed over a longer period (quantitative history surveys). The recall, general, and quantitative history surveys are easly implementated in epidemiologic investigations and are the most useful means of measuring physical activity in large population. These assessment procedures are relative reliable, are inexpensive, and do not generate major selection bias. However, they have some limitations, e.g., recall procedures give too little informations about the dimensions of the physical activity being measured. Some dimensions of physical activity are related to the health state, e.g., energy expenditure is related to obesity (Laporte et al., 1985). For this reason validity and reliability of recall are not often underminet.

Physical activity scores are expressed as ordinal scales of average energy expenditure measurement in kilojules (kJ) or kilocalories (kcal, 1 kcal = 4.18 kJ) per body weight in the time unit (e.g., kcal◊kg-1 body weight◊h-1 or kJ◊kg-1 body weigh◊h-1) during a day, week or month or in units of intensity, i.e., in MET-hours per day or week (MET-h◊day-1, MET-h◊week-1) (Ainsworth et al., 1993, Ainsworth et al., 2000). For example, writing, reading or driving a car result in 75-125 kcal◊h-1 of the average energetic expenditure of an adult, whereas cycling, walking or jogging require of 150-500, 200-250 and 300-500 kcal◊h-1, respectively. Energy expenditure is larger in a hot day, when individuals are heavier, or performe the exercise more vigorously. A MET score classifies specific types of activity as the ratio of the associated metabolic rate for the specific activity to the resting metabolic rate. The second definition of one MET is the energy expenditure for sitting quietly (about 3.5 ml of oxygen◊kg-1 body weight◊min-1, or 1 kcal◊kg-1 body weight◊h-1 or 4.2 kJ◊kg-1 body weight◊h-1 for the average adult (Ainsworth et al., 1993; Ainsworth et al., 2000). According to Compedium of Physical Activities designed by these authors classifying physical activities by the rate of energy expenditure, the intensity of an activity is categorized as multiples of one MET. Examples of intensity codes used in calculation of energy expenditure during physical activity are: e.g., jogging/running 7.0 MET, dancing 4.8 MET, walking 3.5 MET, aerobics 4.5 MET, bicycling 4.0 MET, tenis 6.0-8.0 METs.

In order to increase our knowledge of the beneficial effect of physical activity on cancer incidence complete measurements of physical activity must be used. These measures include all components of physical activity, i.e., occupational work, leisure time (exercise/sports), household activities, and child-care activity throught the subject's lifetime. The literature data show that researchers report mainly results of epidemiological studies basing on individual's self-reports (Klesges et al., 1990), a detailed, standarized interview (administred by interviewers) or a structured questionnaire (Taylor et al., 1978; Kriska et al., 1997; Friedenreich et al., 1998). Physical activity is considered in a different manner. Some authors consider only exercise/sports or only occupational activity, other lifetime activities; also different time periods of subject's lifetime are chosen, e.g., total lifetime, the year before the interview, childhood and adolescence, or adulthood.

In the subject literature a large number of different method for physical activity determination have been proposed for both occupational and recreational activities. In order to classify occupational physical activity researchers usually have used a three – digit occupation code rated by U.S. Department of Labor (1993): individuals are categorized as sedentary when their job requires physical activity less than 20% of the work time; moderate active – 20-80% of the work time, and highly active – more than 80% of the work time. Based on the job activity code and the number of years worked by a person, weighted job activity codes are then accounted following by categorization of participant's physical activity level (see as an example paper of Young et al., 2003). In turn, Friedenreich et al. (1998) in their lifetime record of occupational activities definied as sedentary those activities that require only sitting with minimal walking (e.g. secretary), as light- the activities with minimal physical effort, i.e., standing or slow walking without of perspiration and increase in heart rate (professions in this category includes, e.g., teachers, hairdressers), moderate – the activities that requires carrying light loads (5-10 lb.), continuous walking; these activities would cause perspiration and increase the heart rate, and heavy – the activities such as lifting, carrying heavy load (>10 lb.), brisk walking, i.e., activities increasing the heart rate and causing heavy sweating. In other study occupational physical activity determination was based on questions assessing the frequency of sitting, standing, walking, lifting heavy loads, being tired after work, or on self-reported assessment of physical effort (e.g. Alfano et al., 2002).

The basic difference between studies on occupational and recreational physical activities lies in exposure assessment. In developed countries the job exhibits little difference in the physical effort. In addition, the measurement of physical activity exposure at work has limitations such as variability of physical effort within a job class, misclassification of job intensity, seasonal changes in job effort (e.g., farmers work harder during the summer than during the winter), (Laporte et al., 1985). For this reason majority of epidemiological studies on relation between physical activity and breast cancer risk is interested in assessment of leisure-time physical activity.

The Friedenreich et al's questionnaire (1998) gives a possibility to determine lifetime total physical activity based on lifetime records of: household, occupational and exercise/ sports activities. The formulas allowing to determine average number of hours per week spent in the above mentioned activities throughout a participant's life are reported, and data would be denoted as MET-hours per week.

During estimation of relationship between physical activity and cancer occurrence the contrast in the exposure physical activity versus physical inactivity is considered. Lifestyle can exert a direct influence on cancer incidence and physical activity and may by associated with other healthy behaviours such as smoking, alcohol intake, diet, obesity. These modified factors are also related to cancer development, setting up the potential confounders in estimates of cancer risk.. For this reason in epidemiological studies, e.g., on relation between physical activity and breast cancer risk beside the data colection dealing with physical activity, information gathered during interview included demographic characteristics (age, education level, family income, weight and high), family history of breast and other cancers, medical history, reproductive factors (age at menarche, age at menopause parity, age at first birth, breast feeding, menopause status), alcohol consumption, hormone use history, smoking, and diet for both cases and controls.

Odds ratios for cancer risk in more recently published papers were estimated with a full assessment of confounding and potential risk factors (Thune & Furberg, 2001; Friedenreich & Orenstein, 2002).

Logistic regression models are used to obtain maximum likehood estimates of the ORs or to calculate hazards rate ratios (RR) (e.g., Cox proportional modelling), and associated 95% CI as well as to evaluate the effect of the above mentioned confounding and modifying factors on the relation of physical activity on the breast cancer risk. Descriptive characteristics of cases and controls are compared using t-tests for continuous variables and chi-square analyses for categorical variables.

It is worthwhile mentioning that the accurate measurement of physical activity has been very difficult in epidemiological studies and the techniques used in studies are likely limited by validity and reliability; the correlations between quantitative history survey of physical activity and its direct measure are “rather modest”, however they allow to compare the direction (positive or negative) and magnitude of physical activity influence on cancer development (Laporte et al., 1985; McTiernan et al., 1998). According to recommendations of Powell et al. (1987) the accuracy of physical activity measure may be improved by fulfilment of several criteria, among them are: clearly definied categories of physical activity; accuracy of the activity estimation should be examined in respect of reliability and validity of a measure (for example, questionnaire should be tested in a pilot study preceeding the case-control study); use of the recall calendar during determination of the lifetime total physical activity (e.g., as in Friedenreich et al. study, 1998 for breast cancer or in the Kriska questionnaire for historical leisure activity, Kriska, 1997); physical activity levels should be calculated for the individual woman; the full range of physical activity types should be determined; dose of physical activity requires collection of data on frequency, duration and intensity, using responsible and accurate techniques; physical activity should be examined across a participant's life span. For exhaustive details the reader is referred to the paper of Powell et al. (1987) and Friedenreich & Orenstein (2002).

Possible Biological Mechanisms in the Relation between Physical Activity and Cancer Risk

Cancer is a multifactorial disease and various mechanisms may by operative in cancer inhibition with increased physical activity. These mechanisms may by dependent on a stage of carcinogenesis, cancer site, type of physical activity, and the individual's characteristic.

Various hypothesized mechanisms for the protective effect of physical activity against cancer risk have been extensively reported in literature (see, e.g., McPherson et al., 1994; Thompson, 1994; Colditz et al., 1997; McTiernan et al., 1998; Friedenreich, 2001b; Friedenreich & Thune, 2001; Liehr & Jones, 2001; Friedenreich & Orenstein, 2002; Gerber, 2003; McTiernan, 2003; Quadrilatero & Hoffman-Goetz, 2003; Westerlind, 2003; Atkinson et al., 2004; Borugian et al., 2004; Charkoudian & Joyner, 2004;

Chlebowski et al., 2004; DeLellis et al., 2004; Furberg et al., 2004; McTiernan et al., 2004; Renehan et al., 2004; Sturmer & Manson, 2004 ; Thompson et al., 2004).
The majority of the above mentioned papers reviewed hypothesized mechanisms contributing to the lowered cancer risk by physical activity, which were actively researched.

The main mechanisms include: (a) Increasing gut motility by physical activity; shorted gastrointenstinal transit time may protect against colon cancer by decreasing bowel transit time, followed by less opportunity for carcinogens or cancer promoters contact in the fectal steam and colonic mucosa (Friedenreich & Orenstein, 2002); (b) Influencing levels of prostaglandins; strenuous exercise may increase prostaglandin PGF which acts as an inhibitor of colonic cell proliferation. PGF also increases gut motility. It should be noted that physical activity does not increase levels of prostaglandin PGE2, acting as an enhancer of the rate of colonic cell proliferation; (c) Decreasing levels of insulin and insulin-like growth factors (IGFs), glucose, triglycerides and bile acid secretion or by enhancing the acid metabolism and raising levels of IGF binding proteins (IGFBP-3) and HDL cholesterol (a review of Quadrilatero & Hoffman-Goetz, 2003 and papers cited therein). IGFs are multifunctional peptides that regulate cell differentiation, proliferation and apoptosis. All those IGFs actions and their binding proteins (Kari et al., 1999) are important in tumorigenesis (Renehan et al., 2004). High concentrations of circulating IGF-I are associated with an increased risk of lung (Yu et al., 1999); prostate (Chan et al., 1998), premenopausal breast (Hankinson et al., 1998), and colorectal cancers (Ma et al., 1999), whereas higher concentrations of IGFBP-3 may be associatd with a decreased cancer risks, except for premenopausal breast cancer. Concentrations of IGF-I and IGFBP-3 are dependent on diet and lifestyle factors (Friedenreich, 2001a). Dietary energy restriction may reduce levels of circulating insulin-like growth factors (Thomson et al., 2004). (d) Decreasing time exposure to endogenous sex hormones by delay of menarche, reduction of the number of ovulatory cycles, reduction of ovarian estrogen generation. The study by McTiernan et al. (1999) was the first which showed that the change in physical activity level from low to moderate is accompanied by the reduction in the serum concentrations of estrone, estradiol, testosterone, androstenedione and their relatives. Physical activity modifies metabolic hormone levels by lowering concentration of fat produced estrogens, and may also reduce estrogens by increased production of sex hormone binding globulin in both men and women. Increased physical activity may alterate estrogen metabolism. Estrogens, especially estrone and estradiol exert stimulatory effect on mammary glands (Key et al., 2001, McTiernan et al., 1998). The association between body size, physical activity, menopausal status and breast cancer are very complex. Obesity is one of the strongest determinants of increased endogenous sex hormones concentrations in women after menopause and is considered as a very important risk factor for the breast cancer among postmenopausal women, colon and endometrial cancers. Physical inactivity is a risk for obesity (Carmichael & Bates, 2004). In turn, an increased production of sex hormones binding globulin by exercise may also prevent prostate cancer development because globulin are able to bind to androgens, thereby they decrease levels of plasma testosterone (Hackney et al., 1998). The mechanisms that influence several cancer types include; (a) enhancing the immune system; the immune system is able to recognize and eliminate neoplastic cells. Moderate physical activity may enhance immune function by increasing number and activity of macrophages, lymphokine-activated killer cells and their regulating cytokins (Shephard & Shek, 1998). In turn, long-term or strenuous exercise have been shown to suppres the function of the human immune, as recognized by a reduction in leucocytosis and an impaired functioning of the system; (b) Improving antioxidant property of defense systems; moderate physical activity enhances systems scavenging reactive oxygen species (ROS), for example, oxygen free radicals such as hydroxyl radical, superoxide radical, and peroxyl radical, peroxynitrite and singlet oxygen (an energetically rich form of molecular oxygen). These highly reactive species are responsible for oxidative stress considered as primary factor in various diseases, among them, in carcinogenesis (Feig et al., 1994, Toyokuni et al., 1995). In turn, strenuous exercise can place the body under oxidative stress due to an increased oxygen consumption in vivo followed by increase generation of reactive oxygen species (Ji, 1995). The mentioned species can be highly cytotoxic when produced in excess, thereby they may damage intracellular and extracellular structures (DNA, lipids, proteins) and lead to certain diseases, among them a cancer (for details the reader is referred to the papers of Dreher & Junod (1996), Toyokuni et al. (1995) and Toyokuni et al. (1998). It is worth noting that the use of animal models is important in an understanding of the biological mechanisms operating between exercise and cancer risk. For a substantial review of literature on this topic the reader is referred to the review of Hoffman-Goetz (2003).

Conclusions and Public Health Recommendations for Cancer Prevention

The epidemiological studies on the relation between physical activity and cancer risk have some methodological limitations: Firstly, the limitation may result from a different methods of assessment of physical activity. Measures have ranged from self-reported categories of individual's physical activity to trained interviewers administred structured questionnaires, including information on all episodes of physical activity during leisure time, activities of daily living, active transport and in occupational titles with a complete assessment of dose (i.e., frequency, intensity, and duration) of activity. Most of the studies were based on recent activity, but some studies did determine lifetime activity. Secondly, cancer risk differs across population subgroup (e.g., sex, race, body mass index, menopausal status), therefore the effect of physical activity on cancer outcome may be different within subgroups. Thirdly, the relation between physical activity and cancer risk may be interrelated with other confounding risk factors (e.g. smoking, family history, dietary, or weight maintance).

Although studies on relation between physical activity and the risk of cancer have several potential limitations, animal experimental and epidemiological data provide strong evidence for decreased risk of colon and breast cancer and moderate for prostate, lung, and endometrial cancers with increased levels of physical activity. Moreover, moderate physical activity exerts a positive benefit on health: decreases risk of all cause of mortality, prevents against cardiovascular disease, obesity, and exerts positive effect on mental health (for a recent review see Bauman, 2004). In Western countries the prevalence of physical inactivity is high. As reported by Garret et al. (2004) 74% of American adults failed to meet recommended quidelines for physical activity at least 30 minutes of moderate intensity on most days of the week (5 days per week or more), and 25% are not active at all. This physical effort corresponds with an energy expenditure of about 4200 kJ·week-1 (1000 kcal·week-1) for the average body weight of a women being 65 kg (Oguma et al., 2002) and is suggested as required to postpone early mortality in women. According to guidelines of the Centers for Disease Control and Prevention and the American College of Sports Medicine moderate relative intensity of activity corresponds to from 3 to 6 METs for most young to middle aged adults (Lee et al., 2003). Suggested modes of exercise include brisk walking, swimming, cycling, yard work, house repair.

Currently, there are no differences in recommendation for exercise prescription between men and women. For further details regarding recommended exercise prescription the reader is refered to the edition of the American College of Sports Medicine (2000). The evidence of enhanced metabolism among women with higher body mass levels, including 15-30 minutes of walking per day, found by Mattews et al., (2004) supports this recommendation. Increased physical activity allows to maintain appropriate ratio of weight to height and contributes substantially to the primary prevention of cancer apart from avoidance of tobacco smoke, increased consumption of vegetables and fruits (preferably fresh), reduced consumption of red meat and animal fat (except fish), and refined carbohydrates. It is worth to add that primary and secondary prevention (presymptomatic disease detection at an early stage before the appearance of the symptoms) have reduced mortality from cancer by about 13% (Osborne et al., 1997; Adami et al., 2001). In addition, it is estimated that incidence of cancer mortality would fall by 29% mainly on account of measures of primary prevention.

For some cancer sites, for example, colon, breast, higher levels of physical activity and longer duration are recommended (at least 30-60 min·day-1 of moderate to vigorous intensity, Lee, 2003).

In conclusion, with the high prevalence of individuals being sedentary and since cancer incidence is increasing there is a need to carry more research on the relation between physical activity and cancer in order to clarify type of physical activity performed, at what intensity, duration and frequency, at which time periods in life being most preventive against particular cancer sites.

References

Adami H-O, Day NE, Trichopoulos D, Willett WC (2001). Primary and secondary prevention in the reduction of cancer morbidity and mortality. *Eur J Cancer*, **37**, S118-27.

Ainsworth BE, Haskell WL, Leon AS, et al (1993). Compedium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc*, **1**, 71-80.

Ainsworth BE, Haskell WL, Whitt MC, et al (2000). Compedium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*, **32**, S498-S515.

Ainsworth BE, Sternfeld B, Slattery ML, Daguisé V, Zahm SH (1998). Physical activity and breast cancer. Evaluation of physical activity assessment methods. *Cancer*, **83**, 611-620.

Alfano CM, Klesges RC, Murray DM, Beech BM, McClanahan BS (2002). History of sport participation in relation to obesity and related health behaviours in women. *Prev Med*, **34**, 82-89.

American College of Sports Medicine's Guidelines for Exercise Testing and Prescription. 6th edition. Philadelphia: Franklin, B.A. (editor) Lippincott Williams and Wilkins, 2000.

Atkinson C, Lampe JW, Twaroger SS, et al (2004). Effects of a moderate intensity exercise intervention on estrogen metabolism in postmenopausal women. *Cancer Epidemiol Biomark Prev*, **13**, 868-74.

Bauman AE (2004). Updating the evidence that physical activity is good for health: an epidemiological review 2000-2003. *J Sci Med Sport*, **7 (Suppl 1)**, 6-19.

Borugian MJ, Sheps SB, Kim-Sing C, Vet al (2004). Insulin, macronutrients, and physical activity: are potential indicators of insulin resistance associated with mortality from breast cancer? *Cancer Epidemiol Biomark Prev*, **13**, 1163-72.

Brewster A, Helzlsouer K (2001). Breast cancer epidemiology, prevention, and early detection. *Curr Opin Oncol*, **13**, 420-5.

Carmichael AR, Bates T (2004). Obesity and breast cancer: a review of the literature. *The Breast*, **13**, 85-92.

Caspersen CJ, Powell K, Christenson GH (1985). Physical activity, exercise, and physical fitness: definition and distinctions for health-related research. *Public Health Rep*, **100**, 126-31.

Chan JM, Stampfer MJ, Giovannucci E, et al (1998). Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science*, **279**, 563-6.

Charkoudian N, Joyner MJ (2004). Physiologic considerations for exercise performance in women. *Clin Chest Med*, **25**, 247-55.

Chen C-L, White E, Malone KE, Daling JR (1997). Leisure-time physical activity in relation to breast cancer among young women (Washington, United States). *Cancer Causes Control*, **8**, 77-84.

Cherry TA (1922). A theory of cancer. *Med J Aust*, **1**, 425-438.

Chlebowski RT, Pettinger M, Stefanick ML, et al (2004). Insulin, physical activity, and caloric intake in postmenopausal women: breast cancer implications. *J Clin Oncol*, **22**, 4507-4513.

Colbert LH, Lacey JVJr, Schairer C, et al (2003). Physical activity and risk of endometrial cancer in a prospective cohort study (United States). *Cancer Cases Control*, **14**, 559-67.

Colditz GA, Cannuscio CC, Frazier AL (1997). Physical activity and reduced risk of colon cancer: implications for prevention. *Cancer Causes Control*, **8**, 649-67.

Colditz GA, Feskanich D, Chen WY, Hunter DJ, Willett WC (2003). Physical activity and risk of breast cancer in premenopausal women. *Br J Cancer*, **89**: 847-51.

Collaborative Group on Hormonal Factor in Breast Cancer (2001). Familiar breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease. *Lancet*, **358**, 1389-99.

DeLellis K, Rinald S, Kaaks RJ, et al (2004). Dietary and lifestyle correlates of plasma insulin-like growth factor-I(IGF-I) and IGF binding protein-3(IGFBP-3): the multiethnic cohort. *Cancer Epidemiol Biomark Prev*, **13**, 1444-51.

Dirx MJ, Voorrips LE, Goldbohm RA, van den Brand PA (2001). Baseline recreational physical activity, history of sport participation, and postmenopausal breast carcinoma risk in the Netherlands Cohort Study. *Cancer*, **92**, 1638-49.

Doll R, Peto R (1981). The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst*, **66**, 1191-308.

Dorgan JF, Brown C, Baretti M, et al (1994). Physical activity and risk of breast cancer in the Framingham Heart Study. *Am J Epidemiol*, **139**, 662-669.

Drake DA (2001). A longitudinal study of physical activity and breast cancer prediction. *Cancer Nursing*, **24**, 371-377.

Dreher D, Junod AF (1996). Role of oxygen free radicals in cancer development. Review. *Eur J Cancer*, **32**, 30-38.

Feig DI, Reid TM, Loeb LA (1994). Reactive oxygen species in tumorigenesis. *Cancer Res*, **54**, 1890s-1894s.

Friedenreich CM (2001a). Physical activity and cancer prevention: from observational to intervention research. *Cancer Epidemiol Biomark Prev*, **10**, 287-301.

Friedenreich CM (2001b). Review of anthropometric factors and breast cancer risk. *Eur J Cancer Prev*, **10**, 15-32.

Friedenreich CM (2004). Physical activity and breast cancer risk: the effect of menopausal status. *Exerc Sport Sci Rev*, **32**, 180-4.

Friedenreich CM, Courneya KS, Bryant HE (1998). The lifetime total physical activity questionnaire: development and reliability. *Med Sci Sports Exerc*, **30**, 266-274.

Friedenreich CM, McGregor SE, Courneya KS, Angyalfi SJ, Elliott FG (2004). Case-control study of lifetime total physical activity and prostate cancer risk. *Am J Epidemiol*, **159**, 740-749.

Friedenreich CM, Orenstein MR (2002). Physical activity and cancer prevention: etiologic evidence and biological mechanism. *J Nutr*, **132**, 3456S-64S.

Friedenreich CM, Rohan TE (1995). A review of physical activity and breast cancer. *Epidemiology*, **6**, 311-7.

Friedenreich CM, Thune I (2001). A review of physical activity and prostate cancer risk. *Cancer Causes Control*, **12**, 461-75.

Furberg A-S, Veierod MB, Wilsgaard T, Bernstein L, Thune I (2004). Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. *J Natl Cancer Inst*, **96**, 1152-60.

Gammon MD, John EM, Britton JA (1998). Review. Recreational and occupational physical activities and risk of breast cancer. *J Natl Cancer Inst*, **90**, 100-117.

Garret NA, Brasure M, Schmitz KH, Schultz M, Huber MR (2004). Physical inactivity. Direct cost to a health plan. *Am J Prev Med*, **27**, 304-9.

Gerber B, Mylonas I (2003). Reduction of the risk of breast cancer. *Zentralbl Gynakol*, **125**, 6-16.

Gotay K (2005). Behavior and cancer prevention. *J Clin Oncol*, **23**, 301-10.

Hackney AC, Fahrnes CL, Gulledge TB (1998). Basal reproductive hormonal profiles are altered in endurance trained men. *J Sports Med Phys Fitness*, **38**, 138-41.

Hamajima N, Hirose K, Tajima K, et al (2002). Alcohol, tabacco and breast cancer-collaborative reanalysis of individual data from 53 epidemiologic studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer*, **87**, 1234-45.

Hankinson SE, Willett WC, Colditz GA, et al (1998). Circulating concentrations of insulin- growth factor- I and risk of breast cancer. *Lancet*, **351**, 1393-6.

Hardman AE (2001). Physical activity and cancer risk. *Proc Nutr Soc*, **60**, 107-13.

Hirose K, Hamajima N, Takezaki T, Miura S, Tajima K (2003). Physical exercise reduces risk of breast cancer in Japanese women. *Cancer Sci*, **94**, 193-9.

Hoffman-Goetz L (2003). Physical activity and cancer prevention: animal-tumor models. *Med Sci Sports Exerc*, **11**, 1828-33.

Hulka BS, Moorman PG (2001). Breast cancer: hormones and other risk factors. *Mauritas*, **38**, 103-16.

IARC. Weight Control and Physical Activity 2002. 6 IARC Press Lyon, France.

Jemal A, Murray T, Samuels A, et al (2003). Cancer Statistics, 2003. *CA-A Cancer J Clin*, **53**, 5-26.

Ji LL (1995). Oxidative stress during exercise: implication of antioxidant nutrients. *Free Radic Biol Med*, **18**, 1079-86.

John EM, Horn-Ross PL, Koo J (2003). Lifetime physical activity and breast cancer risk in a multiethnic population: the san Francisco Bay area breast cancer study. *Cancer Epidemiol Biomark Prev*, **12**, 1143-52.

Kari FW, Dunn SE, French JE, Barrett JC (1999). Role for insulin-like growth factor-1 in mediating the anti-carcinogenetic effect of caloric restriction. *J Nutr Health Aging*, **3**, 92-101.

Kelsey JL, Gammon MD (1991). The epidemiology of breast cancer. *CA-A Cancer J Clin*, **41**, 147-65.

Key TJ, Verkasalo PK, Banks E (2001). Epidemiology and breast cancer. *Lancet Oncol*, **2**, 133-40.

Key TJ, Allen NE, Spencer EA, Travis RC (2002). The effect of diet on risk of cancer. *Lancet*, **360**, 861-8.

Klesges RC, Eck LH, Mellon MW, et al (1990). The accuracy of self-reports of physical activity. Med Sci Sports Exer : 22: 690-7.

Kriska AM (1997). Historical leisure activity questionnaire. *Med Sci Sports Exer*, **29(Suppl)**, S43-5.

Kruk J (2002). Physical activity and risk of breast cancer. *Biol Sport*, **19**, 3-32.

Kruk J (2005). Physical activity and breast cancer. In: Ransdell L. & Petlichkoff L (eds.) Ensuring the Health of Active and Athletic Girls and Women. Reston, VA: National Association for Girls and Women in Sport U.S.

Kubik A, Zatloukal P, Tomasek L, et al (2004). Lung cancer risk among non-smoking women in relation to diet and physical activity. *Neoplasma*, **51**, 136-43.

Kushi L, Giovannucci E (2002). Dietary fat and cancer. Am J Med : 113(9B): 63S-70S.

Lagerros YT, Hsieh SF, Hsieh CC (2004). Physical activity in adolescence and young adulthood and breast cancer risk: a quantitative review. *Eur J Cancer Prev*, **13**, 5-12.

Laporte RE, Montoye HJ, Caspersen CJ (1985). Assessment of physical activity in epidemiologic research: problems and prospects. *Public Health Reports*, **100**, 131-46.

Latikka P, Pukkala E, Vihko V (1998). Relationship between the risk of breast cancer and physical activity. An epidemiological perspective. *Sports Med*, **26**, 133-43.

Lee I-M, Cook NR, Rexrode KM, Buring JE (2001a). Lifetime physical activity and risk of breast cancer. *Br J Cancer*, **85**, 962-5.

Lee IM, Rexrode KM, Cook NR, Hennekens CH, Buring JE (2001b). Physical activity and breast cancer risk: the Women's Health Study (United States). *Cancer Causes and Control*, **12**, 137-45.

Lee I-M (2003). Physical activity and cancer prevention – data from epidemiologic studies. *Med Sci Sports Exerc*, **11**, 1823-7.

Lee IM, Sesso HD, Oguma Y, Paffenbarger RS (2003). Relative intensity of physical activity and risk of coronary heart disease. *Circulation*, **107**, 1110-6.

Levi F, La Vecchia C, Negri E, Franceschi S (1993). Selected physical and the risk of endometrial cancer. *Br J Cancer*, **67**, 846-51.

Liehr JG, Jones JS (2001). Role of iron in estrogen induced cancer. *Curr Medicinal Chem*, **8**, 839-49.

Litman AJ, Nojgt LF, Beresford SA,Weiss NS (2001). Recreational physical activity and endometrial cancer risk. *Am J Epidemiol*, **154**, 924-33.

Ma J, Pollak MN, Giovannucci E, et al (1999). Prospective study of colorectal cancer risk in men and and plasma levels of insulin – like growth factor IGF-I and IGF-binding-3. *J Natl Cancer Inst*, **91**, 620-5.

Mao Y, Pan S, Swen SW, Johnson KC (2003). Canadian Registries Epidemiology Research Group. Physical activity and the risk of lung cancer in Canada. *Am J Epidemiol*, **158**, 564-75.

Matthews CE, Fowke JH, Dai Q, et al (2004). Physical activity, body size, and estrogen metabolism in women. *Cancer Causes Control*, **15**, 473-81.

McPherson K, Steel CM, Dixon JM (1994). Breast cancer-epidemiology, risk factors and genetics. *Br Med J*, **309**, 1003-6.

McPherson K, Steel CM, Dixon JM (2000). Breast cancer-epidemiology, risk factors and genetics. *Br Med J*, **321**, 624-8.

McTiernan A (2003a). Behavioral risk factors in breast cancer: can risk be modified? *The Oncologist*, **8**, 326-34.

McTiernan A (2003b). Intervention studies in exercise and cancer prevention. *Med Sci Sport Exerc*, **35**, 1841-5.

McTiernan A, Tworoger SS, Ulrich CM, et al (2004). Effect of exercise on serum estrogens in postmenopausal women: a 12-month randomized clinical trial. *Cancer Res*, **64**, 2923-8.

McTiernan A, Ulrich D, Slate S, Potter J (1998). Physical activity and cancer etiology: association and mechanisms. *Cancer Causes Control*, **9**, 487-509.

McTiernan, Urlich C, Yancey D, et al (1999). The physical activity for total health (PATH) study: rationale and design. *Med Sci Sports Exerc*, **31**, 1307-12.

Mona O, McCarron P, Gunnell D, Smith GP (2003). Exposures in child, adolescence and early adulthood and breast cancer risk: a systematic review of the literature. *Breast Cancer Res Treat*, **78**, 223-76.

Moradi T, Adami HO, Erbom A, ET AL (2002). Physical activity and risk for breast cancer a prospective cohort study among Swedish twins. *Int J Cancer*, **100**, 76-81.

Moradi T, Nyren O, Bergstrom R, et al (1998). Risk for endometrial cancer in relation to occupational physical activity: a nationwide cohort study in Sweden. *Int J Cancer*, **7**6, 665-70.

Moradi T, Weiderpass E, Signorello LB, et al (2000). Physical activity and postmenopausal endometrial cancer risk (Sweden). *Cancer Causes Control*, **11**, 829-37.

Murthy NS, Mathew A (2004). Cancer epidemiology, prevention and control. *Curr Sci*, **86**, 518-27.

Oguma Y, Sesso HD, Paffanbarger RSJr, Lee I-M (2002). Physical activity and all cause mortality in women: a review of evidence. *Br J Sports Med*, **36**, 162-72.

Okasha M, McCarron P, Gunnell D, Smith GD (2003). Exposures in childhood, adolescence and early adulthood and breast cancer risk: a systematic review of the literature. *Breast Cancer Res Treat*, **78**, 223-276.

Osborne M, Boyle P, Lipkin, M (1997). Cancer prevention. *Lancet*, **349(Suppl)**, 27-30.

Parkin DM, Bray F, Ferlay J, Pisani P (2001). Estimating the world cancer burden: Globocan 2000. *Int J Cancer*, **94**, 153-6.

Patel AV, Calle EE, Bernstein L, Wu AH, Thun MJ (2003a). Recreational physical activity and risk of postmenopausal breast cancer in a large cohort of US women. *Cancer Causes Control*, **14**, 519-29.

Patel AV, Press MF, Meeske K, Calle EE, Bernstein L (2003b). Lifetime recreational exercise activity and risk of breast carcinoma in situ. *Cancer*, **98**: 2161-9.

Perkins MA, Dicken P, Hyde DJ, Grant LJ (1995). Two miniature monitors for long-term ambulatory studies. *Med Engin Phys*, **17**, 410-5.

Powell KE, Thompson PD, Caspersen CJ, Kendrick JS (1987). Physical activity and the incidence of coronary heart disease. *Ann Rev Public Health*, **30**, 266-74.

Pukkala E, Poskiparta M, Apter D, Vihko V (1993). Life-long physical activity and cancer risk among Finnish female teachers. *Eur J Cancer Prev*, **2**, 369-76.

Quadrilatero J, Hoffman-Goetz L (2003). Physical activity and colon cancer. A systematic review of potential mechanisms. *J Sport Med Phys Fitness*, **43**, 121-38.

Renehan AG, Zwahlen M, Minder C, et al (2004). Insulin-like growth (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet*, **363**, 1346-53.

Schlesselman JJ, Stolley PD (1982). Case-Control Studies. Design, Conduct Analysis : 177: New York, Oxford, Oxford University Press 32-4.

Shepard RJ, Shek PN (2002). Association between physical activity and susceptibility to cancer. Possible mechanisms. *Sport Med*, **26**, 293-15.

Sivertsen I, Dahlstrom AW (1998). The relation of muscular activity to carcinoma. A preliminary report. *J Cancer Res*, 1922??, **6**, 365-78.

Slattery ML (2004). Physical activity and colorectal cancer. Sports Med : 34: 239-52.

Slattery ML, Edwards S, Curtin K, et al (2003). Physical activity and colorectal cancer. *Am J Epidemiol*, **158**, 214-24.

Slattery ML, Potter JD (2002). Physical activity and colon cancer: confounding or interaction? *Med Sci Sports Exerc*, **34**, 913-9.

Stein CJ, Colditz GA (2004). Modifiable risk factors for cancer. *Br J Cancer*, **90**, 299-303.

Steindorth K, Schmidt M, Kropp S, Chang-Claude J (2003). Case-control study of physical activity and breast cancer risk among premenopausal women in Germany. *Am J Epidemiol*, **157**, 121-30.

Sturmer T, Manson JE (2004). Estrogens and breast cancer: does timing really matter? *J Clin Epidem*, **57**, 763-5.

Taylor HL, Jacobs DR Jr, Schucker B, et al (1978). A questionnaire for the assessment of leisure time physical activities. *J Chron*

Dis, **31**, 741-55.
Terry P, Baron JA, Weiderpass E, et al (1999). Lifestyle and endometrial cancer risk: a cohort study from the Swedish Twin Registry. *Int J Cancer*, **82**, 38-42.
Thompson HJ (1994). Effect of exercise intensity and duration on the induction of mammary carcinogenesis. *Cancer Res*, **54 (Suppl)**, 1960s-3s.
Thompson HJ, Zhu Z, Jiang W (2004). Weight control and breast cancer prevention: are the effects of reduced energy intake equivalent to those of increased energy expenditure? *J Nutr*, **134**, 3407S-11S.
Thune I, Furberg AS (2001). Physical activity and cancer risk: dose-response and cancer, all sites and site-specific. *Med Sci Sports Exerc*, **33**, S530-50.
Toyokuni S (1998). Oxidative stress and cancer: the role of redox regulation. *Biotherapy*, **11**, 147-54.
Toyokuni S, Okamoto K, Yodoi J, Hiai H (1995). Hypothesis. Persistent oxidative stress in cancer. *Fed Eur Biochem Soc Lett*, **353**, 1-3.
U.S. Department of Labor (1993). Selected characteristics of occupations defined in the Revised Dictionary of Occupational Titles. Washington, D.C. U.S. Government Printing Office.
Westerlind KC (2003). Physical activity and cancer prevention-mechanisms. *Med Sci Sports Exerc*, **35**, 1834-40.
Willer A (2003). Reduction of the individual cancer risk by physical exercise. *Oncologie*, **26**, 283-9.
World Cancer Research Fund / American Institute for Cancer Research (1997). Food, nutrition and the prevention of cancer: A global perspective. Washington D.C.: American Institute for Cancer Research.
Young D, Bernstein L, Wu AH (2003). Physical activity and breast cancer risk among Asian-American women in Los Angeles. A case-control study. *Cancer*, **97**, 3565-75.
Yu H, Spitz MR, Mistry J, et al (1999). Plasma levels of insulin-like growth factor-I and lung cancer risk: a case-control analysis. *J Natl Cancer Inst*, **91**, 151-6.