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Title: Cancer risk in Norwegian elite athletes

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Cancer risk in athletes

During the last two decades, there has been an increasing focus on beneficial effects of physical activity in cancer development. The evidence is convincing only for colon cancer (1). A probable inverse relationship has been established for postmenopausal breast cancer and endometrial cancer, whereas limited evidence exists for lung, pancreas and premenopausal breast cancer (1). Physical activity is suggested reduce the risk or delay the onset of cancer diseases. This hypothesis has biological plausibility as physical activity is observed to influence several processes and mechanisms related to cancer (2) and the cancer inhibiting effect might be more significant than previously observed. On the other hand, strenuous exercise maintained for prolong periods has been shown to suppress immunological mechanisms (3), and to adversely influence androgen hormone levels in males (4) and thyroid function in females (5). These effects may increase the risk of selected cancer forms.

The present study aims to investigate whether the level of physical activity influences the cancer risk, using a study population of Norwegian elite athletes, active in the period 1936-2006. As the various athletic disciplines require different activity at varying intensities, this cohort is well suited to study whether there is a dose-response relationship between physical activity and cancer or a threshold limit for effect. To elucidate variations, cancer risks in subgroups of athletes were compared to risk in the general Norwegian population, and to each other.

The present of previously observed inverse relationships between physical activity and cancer were explored. Cancer forms of particular interest were colon-, breast-, lung-, and pancreas cancer, in addition to sex-specific cancer sites. Whether athletes with the most strenuous activity levels have elevated risks of malignant diseases was also investigated.

Cancer forms of interest in this regard were lymphoma, leukemia, testicular- and thyroid cancer.

SUBJECT AND METHODS

Study cohort

The study cohort includes male and female elite athletes. All have represented Norway, in international championships (team or individual disciplines) and/or placed top three in national championship (individual disciplines only), during the period 1936-2006. All participants were active as senior athletes (age ≥ 17). All Olympians were identified from two publications of Norwegian Olympic history (6,7). Participants in other international or national championships were recruited from ranking- or result lists or from the Norwegian Olympic and Paralympic Committee and Confederation of Sports (NIF) discipline-specific annuals. The identification was performed in collaboration with local sport clubs, veterans and sport enthusiasts using the National Population Register. All Norwegian residents alive after 1st January 1960 have been assigned a unique personal identification number (PIN). Persons who were dead before this date were not included. Altogether, 6 124 elite athletes were identified. Information about place of residence, vital status and dates of emigration were obtained through a linkage with the National Population Register. All athletes with a Norwegian address were sent an inquiry to participate and were asked to fill in a questionnaire (n = 5 874). For dead athletes, the questionnaire was addressed to the next of kin (n = 381). Non-respondents were sent a reminder after six weeks. The Directorate of Health gave a permission to include deceased athletes, with non-responding relatives (n = 270). 258 persons were not available for contact as the registered address was incorrect. In total, 3 427 athletes were thus included in the final study cohort, 3 154 with and 270 without a questionnaire (Figure 1).

Cancer information was obtained by a linkage to the Cancer Registry. All incident cancer cases in Norway have been registered by the Cancer Registry since 1952, and reporting is compulsory. Follow-up ended at date of diagnosis, emigration, death or December 31st 2007, whichever occurred first.

Questionnaire

A questionnaire was used to collect information about physical activity (frequency, duration and intensity) during childhood, adolescence, during and after the sports career, during pregnancy (females) and during any cancer disease. The athletes were also asked report alcohol habits, tobacco use, attained educational level, anthropometric measures (during life), onset of puberty, skin type and sunburn episodes, parity and certain health problems of particular interest. In addition, the females were asked about their menstrual cycle, menstrual status and hormone use. (Footnote: The questionnaire is available upon request)

Physical activity assessment

The athletes, endorsed in structured exercise during childhood, adolescence and adulthood. They are, however, a diverse group with regard to discipline, time period of sport career and level of lifetime activity. The type of activity and the performance required to reach an elite level within the different disciplines vary. The athletes were therefore divided into three mutually exclusive categories according to sport discipline: endurance-, power/technique- or ball games. During the last decades, the frequency, duration and intensity of the exercise have increased to meet the elevated performance required in elite sport. The athletes were thus categorized in two subgroups: sport career < 1975 or \geq 1975. The

questionnaire gave information about lifetime activity level (childhood, adolescence, during and after the athletic career). This information was used to categorize the athletes into three different levels of lifetime activity: low, medium or high.

Statistical Analyses

The person years at risk and the observed number of cancer cases were counted by 10-year age groups (20-29, 30-39.....,70-79, 80+), separately for six calendar periods (1953-1961, 1962-1971, ..., 2002-2006). The expected number of cancer cases was calculated by multiplying the number of person-years in each age-group and calendar period by the corresponding cancer incidence rates in Norway during the period of observation. The cancer incidence in the athlete groups were thus compared with that of the general population by the standardized incidence ratio (SIR). The SIRs were calculated by dividing the observed number of the specific cancer cases by the expected number (same age, period and sex). The 95% confidence intervals (CIs) for the SIR were based on the assumption that the number of observed cases was Poisson distributed. For internal comparisons, Poisson regression models were used to estimate incidence rate ratios (IRR) for the association between athletic groups and cancer risk. Age and calendar period were included in all models. In analyses not stratified by sex, also sex was included in the models. All statistical analyses were conducted in STATA (8). A 5% level of significance was used.

RESULTS

Table 1 presents the athletic cohort according to sex, sports discipline, career period, and selected characteristics obtained from the questionnaire. The composition of the study cohort did not differ from the invited cohort regarding either sex, sports discipline or career period. Mean age at response of the survey was 47.6 years and mean age at career closure was

28.5 years. Birth- and adult anthropometry (at age 20) was similar to that of the Norwegian population, although the male athletes were slightly taller (9). The majority of the participants reported to be never users of tobacco (smoke/snuff). Age at onset of beard and voice change was used as an indication of the age of puberty in male athletes. Compared to the general female population (10), a 0.6 years higher median age at onset of menarche was observed in the female athletes. About 30% of the males and 40% of the females were childless. The females' use of hormones was primarily for fertility regulation. Any menstrual irregularities were infrequently reported among females. As most female athletes were premenopausal, pre- and postmenopausal breast cancer risk was not assessed separately in the risk analyses.

Table 2 presents SIR analyses for the study cohort, related to the general population. Significantly lower risks of total cancer (10%), lung cancer (45%) and leukemia/lymphoma (26%) were observed in the athlete cohort. In females, a threefold risk of thyroid cancer was observed compared to the general female population.

Sports discipline

Table 2 also presents SIR analyses stratified by discipline groups. Male endurance athletes, have a statistical significant reduced risk of total cancer, but they also have a significant increased risk of testicular and pancreatic cancer. No significant differences in cancer risk were seen for females in the endurance category. Compared to the general population, no differences are seen for the technique/power athletes, except for a significantly increased risk of thyroid cancer in females. Compared to the general population, the ball practitioners have a reduced risk of total cancer. A significant risk reduction is also seen for colon cancer and for lymphoma/leukemia, although there were few cases. For the sex-specific

cancer forms, no differences were seen between the athletes in the ball game category and the general population.

Career period

For athletes competing prior to 1975, an overall reduced risk of cancer was observed, restricted, however, to males (Table 3). Also the risk of lung cancer was significantly reduced. For female athletes competing from 1975, a reduced risk of female-specific cancer forms was observed, while the risk of thyroid cancer was significantly elevated (Table 3). In males, a twofold risk of testicular cancer was observed.

Lifetime activity level

Table 4 presents estimates from the external analyses, stratified by levels of lifetime activity. Compared to the general population, no significant differences were observed between athletes with a low lifetime activity level and the general population. For the medium category, a reduced risk for total cancer was seen. Although few cases of lung cancer and of lymphoma/leukemia were observed in the study cohort, a significantly reduced risk of these cancer forms was observed. Furthermore, the females had a reduced risk of breast cancer and the female cancer forms combined, but the SIR for thyroid cancer was significantly elevated. The risk of total cancer was also reduced for athletes in the high level, although not significantly so for females. The results for the “unknown” category, mainly consisting of deceased athletes, show an elevated risk of total cancer and female cancer forms.

Internal analyses

Table 5 presents results from the internal analyses, displaying potential differences in risk of total cancer between various subgroups of athletes. The apparently reduced cancer risk

observed in the ball game subgroup was supported by results from the Poisson regression model. The Poisson regression model, however, did not reveal any difference in cancer risk between athletes for the two career periods. The results show a significantly reduced cancer risk for the medium and high lifetime activity levels, compared to the low level, although the large group of unknown precludes a sound interpretation of this result.

DISCUSSION

The associations between physical activity and cancer risk have been explored in a cohort consisting of world class athletes. The risk of total cancer was moderately reduced in the athletic cohort compared to the general population. Stronger significant effects were observed for the specific cancer forms, when analyzing subgroups of athletes separately. The different results in the subgroups may indicate that there exists a threshold level in the effect of physical activity. Ball disciplines are associated with frequent activity of moderate intensity, which also characterize athletes in the medium lifetime activity level. This activity pattern seems to reduce the risk of several cancer forms. The endurance category consists of disciplines that require frequent activity at high intensity levels, which also characterize athletes in the high lifetime activity level. The results for the endurance category indicate that this activity pattern, maintained for years, may increase the risk of selected cancer forms. The technical/power category is very heterogeneous regarding sport disciplines and activity levels, which might explain the unclear risk pattern observed for this subgroup. For the low lifetime activity category, no differences in cancer risk were seen compared to the general population, which might be due to the weak contrast on physical activity.

An inverse relationship between physical activity and cancer risk exists for colon cancer, while a probable relationship is suggested for postmenopausal breast cancer and

endometrial cancer (1). In the present study, a significantly reduced risk of colon cancer was observed, but only in the group of ball practitioners (Table 2). The results indicate that frequent physical activity at a relatively high intensity level, here categorized as moderate, may reduce the risk of colon cancer. Similar observations have been reported by Friedenreich and colleagues in a large cohort study from the European Prospective Investigation into Cancer and Nutrition (11). They therefore suggest daily activity for at least one hour with intensity at a vigorous level to prevent cancer, which should fit well with the activity pattern in most ball disciplines.

A large number of studies have investigated the role of physical activity in the etiology of breast cancer, and the results vary according to different subgroups of females (12). In the present study, we observed a reduced risk of breast cancer, but only in females at the medium level of lifetime activity (Table 3). However, when analyzing the risk of hormone related cancer forms as a group, including breast cancer, also a decreased risk was seen in the group of female athletes who practiced after 1975 (Table 5). Friedenreich and colleagues discuss the most beneficial type, dose and timing of activity for breast cancer risk. They observed the greatest risk reductions at vigorous intensity levels of recreational activity and conclude that lifetime activity is of major importance (11). Based on their statements, we should at the present expect reduced risk of breast cancer in the females at the high level of lifetime activity as well. However, activity levels categorized as “vigorous” in population based studies may still not be comparable with the activity levels categorized as “high” in this cohort of elite athletes. The present results indicate that levels categorized as “moderate” in athletes, maintained for a long period of life, is an optimal activity level to reduce the risk of breast cancer. The decreased risk seen in females, who performed after 1975, may also be due to their activity pattern. As the physical requirements within elite sports have increased over

time and a sedate lifestyle has been more common in the general population, the contrast in activity level between these athletes and the general females may be larger than for former athletes. The protective effect of a full-term pregnancy is well established within breast cancer epidemiology (13,14) and, thus, separate analyses for nulliparous and parous women were performed. The results indicate a preventive effect from childbirths, although the differences were not statistically significant (not shown). Physical activity is suggested to decrease the risk of breast cancer through a delayed onset of menarche (15). Separate analyses, by age at onset of menarche (≤ 13 or >13 years), support this suggestion, as the reduced cancer risk were restricted to females aged >13 years at onset (not shown).

The impact of tobacco smoking on the risk of lung cancer has been described in numerous studies. Although 90% of all incident male cancer cases are attributed to smoking (16), physical activity is observed to influence the risk of lung cancer in a beneficial way (17-19). In 2000, Pukkala and colleagues presented results from a cohort study of Finnish male elite athletes (18). A reduced risk for total cancer and smoke-related cancer forms was observed, in particular within endurance disciplines. In the present study, a similarly low risk of lung cancer was observed, in line with the low percentage of ever smokers. More infrequent smoking among the athletes might not be the only reason for the low risk observed, as ever smoking athletes also tended to have a lower risk than expected (not shown). Physical activity improves ventilation and perfusion, which can reduce the concentration of carcinogens in the airways and the duration of potential adverse exposure, and it may thus decrease the cancer risk (17). Both smoking habits and physical activity can thus explain our results. We were not able to control for variables as occupational exposures or air pollution, which also may play a role in the etiology of lung cancer.

As the proportion of smokers in Norway has decreased, the use of the smokeless tobacco products has increased. Snuff is the major product in use. In the present cohort, the proportion of ever snuff users corresponds with the proportion of users in the general Norwegian population (20). The risk of total cancer in ever snuff users was similar to that of the general population, and no elevated risk for cancer forms previously related to snuff (21) was observed (not shown). In never snuff users, a significantly reduced risk of total cancer was observed. Never use of tobacco products might thus be an indication of a particular awareness concerning a healthy lifestyle.

Extensive physical activity has been suggested to depress immunological mechanisms and increase the susceptibility to infections (3,22), which might increase the risk of cancer (23). Epstein-Barr virus infections developing into mononucleosis have been associated with an increased risk of lymphoma (24,25). In the present cohort, a relatively high incidence of mononucleosis was reported (8.2%), which may indicate a high susceptibility to infections. Nevertheless, a reduced risk of leukemia/lymphoma was shown, and the results are in line with previous observations (26,27). Although the decrease in cancer risk was significant only for athletic groups with moderate intensity levels, the trend seems present for all subgroups, except for that of the low lifetime activity level.

Surprisingly, we observed an elevated risk of thyroid cancer in the female athletes. The number of cancer cases was, however, small. The highest risk was observed in the category of technique/power disciplines, but this risk pattern was consistent for all subgroups. Few strong risk factors have been identified for thyroid cancer, except for irradiation and benign thyroid diseases (28). The incidence rates in females are higher than in males, and the female sex hormones have thus been suggested to play a role (29). Although an inverse

relationship has been observed between physical activity and thyroid cancer (30), endurance exercise has been observed to cause mild hypothyroidism (5,28), and benign thyroid diseases have been suggested to influence the cancer risk (31). In the present study, the females frequently reported symptoms of thyroidal dysfunction (n = 48), which may support the association between physical activity and thyroidal stress. Thyroid dysfunction caused by moderate or strenuous activity, maintained over time, may thus explain of the elevated cancer risk observed.

A reduced risk of testicular cancer was expected in this cohort, due to previous observations and the suggested mechanisms of physical activity (32-34). Although the number of cases was few, an elevated risk of testicular cancer was seen in endurance athletes, but restricted to males who performed from 1975. The only established risk factors of testicular cancer are cryptorchidism and a family history of testicular cancer (35), but inguinal hernias may also play a role in the cancer process (36). Information about cryptorchidism and hernias were obtained from the questionnaire. These factors could not, however, explain the results. Age at onset of puberty (37) and trauma or injuries (32,38) have been suggested to influence the cancer risk. Our finding was neither associated with onset of puberty nor disciplines closely to trauma or injuries. Sex hormones may play a central role in the aetiology of this malignancy (39) and physical activity is suggested to influence cancer development through hormonal mechanisms (40). As strenuous exercise might influence both basal and acute androgen levels (41) and also have immunosuppressive effects (3,42), these factors might explain the present observation. Moderate to strenuous physical activity during adolescence has previously been associated with a similar increase in testicular cancer risk (41).

In male endurance athletes, a twofold risk of pancreatic cancer was observed. Although little is known about the etiology of pancreatic cancer, tobacco use (43), impaired glucose tolerance and insulin resistance (44) are suggested to play important roles. Physical activity is suggested to lower the risk by regulating the glucose metabolism, and by preventing obesity and diabetes (44). The present results can hardly be attributed tobacco use, as the cases mainly report to be never users. Neither does information from the questionnaire relate this result to obesity or diabetes. Further investigation is required to clarify whether strenuous activity may increase the risk of this disease.

Physical activity is suggested to protect against endometrial cancer (1). In the present study, no significant differences were seen. Only three cancer cases were observed among the female athletes. For prostate cancer, the relationship between physical activity and cancer is rather unclear. Physical activity can, however, reduce the level of testosterone and insulin and also increase the production of oxidative enzymes, which are mechanisms that may be involved in the development of this malignancy (1). In the present study, no differences in risk of prostate cancer were observed between the athletes and the general male population.

Lifetime physical activity is difficult to measure. In large studies, occupations, interviews and questionnaires have been the available tools to measure the activity level. Although these methods have benefits, the risk of misclassification is present. In this cohort of elite athletes, the level of physical activity was prospectively assessed by using individual information of discipline and career period. As the performance at elite levels require systematic exercise over time, this inclusion criteria reduces the risk of misclassification. Nevertheless, we also collected information about lifetime activity retrospectively, through a questionnaire. This subjective reporting of frequency and intensity level, over a long time

span, increases the risk of misclassification of lifetime activity. The response rate for the survey was 58.3%, but it did not appear to introduce major selection on sex, discipline or career period (Table 1). Another issue is that previous cancer cases could be more prepared to participate in such a study, which could introduce a selection bias. If so, the cancer cases most likely should be distributed equally in the athletic groups. However, the regression analyses performed to estimate risk differences between the athletic subgroups, showed risk differences that do not support such selection bias. The inclusion of deceased athletes resulted in a group with “unknown” lifetime activity. They represent a large number of cancer cases, and an elevated cancer risk present here. Although this makes it difficult to interpret the results according to this variable, the results strengthen the observations from the two more objective activity variables; discipline and career period.

To conclude, our results support the hypothesis that systematic physical activity reduces the risk of cancer. An elevated risk of selected cancer forms were, however, seen in subgroups of athletes, and the observed relationships indicate a threshold limit for effect rather than a dose-response relationship between physical activity and cancer risk. The most beneficial effect was seen in athletes with activity at moderate intensity levels (ball disciplines/moderate lifetime level). Activity guidelines for cancer prevention might, nevertheless, be geared towards this activity pattern. As the results presented here are specific to a particular group of exercisers, they should be repeated in similar and larger cohorts.

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