Physical Activity and the Risk of Pneumonia in Male Smokers Administered Vitamin E and β-Carotene

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Abstract

It has been proposed that moderate exercise may enhance the immune system. We evaluated whether physical activity at work or at leisure is associated with the risk of pneumonia, and whether the antioxidants vitamin E and β-carotene affect pneumonia risk in physically active people. A cohort of 16 804 male smokers aged 50 – 69 years and working at study entry was drawn from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, which examined the effect of vitamin E, 50 mg/day, and β-carotene, 20 mg/day, on lung and other cancers. Physical activity at work, and the type of leisure-time exercise, were recorded at study entry. We retrieved the first occurrence of hospital-treated pneumonia during a 3-year follow-up from the National Hospital Discharge Register (133 cases). Physical activity at work and at leisure had no association with the risk of pneumonia. In participants with physically loading jobs, neither vitamin E nor β-carotene affected the risk of pneumonia. In participants carrying out moderate or heavy exercise at leisure, β-carotene had no effect, but vitamin E reduced the risk of pneumonia by 50% (95 % CI: 16 – 70%). Previously, exercise has been shown to affect diverse laboratory measures of the immune system which are, however, only surrogate markers for the resistance to infections. The lack of association between physical activity and the risk of pneumonia observed in our study emphasizes the problem of drawing conclusions from surrogate end points. The finding that vitamin E reduced the risk of pneumonia in persons carrying out leisure-time exercise warrants further study.

Introduction

It has been proposed that moderate exercise might improve the immune system, whereas excessive exertion or training may harm the immune system, such that the relationship between physical activity and the risk of infections would follow a "J"-shaped curve [16,21,26,30]. The first part of this curve, the reduction in the risk of infections, is based on studies that found diverse effects, assumed to be positive against infections, with an impact on the immune system with moderate exercise. Previously, we found in a large-scale cohort study that the risk of the common cold was not reduced with an increase in physical activity from the sedentary level [9], but a smaller recent cohort study found a 20 % lower risk of the common cold in subjects carrying out physical activity [14].

The second part of the "J"-shaped curve, the increase in the risk of infections by too heavy exertion, is supported by studies with marathon runners and other subjects undergoing particularly heavy regular training [16,21,26,30]. Nevertheless, it is not obvious that respiratory symptoms occurring after a marathon run are necessarily caused by a viral infection, as they can result from severe mechanical stress caused by several hours of exceptional ventilatory exertion. More specific support of the notion that heavy exertion may increase the risk of respiratory infections comes from studies of military recruits. High rates of pneumonia are a common problem among military recruits and a large study found a 30 times higher risk of hospital admission for pneumonia in Navy and Marine recruits compared with non-recruits [20]. Also, Navy and Marine personnel with less than 1 year of service were at 5 times higher risk of pneumonia than their peers with 4 or more years of service [3]. As an outcome, pneumonia is a substantially less ambiguous infection compared with respiratory symptoms after a marathon run. Heavy exertion is a characteristic feature of military recruits and may contribute to the elevated risk of pneumonia, although crowding of young adults from widely dispersed geographic areas may also contribute to the elevated risk.

There is much evidence indicating that heavy exercise causes oxidative stress in the body [13, 19,25], even though several studies on this topic are technically problematic [12]. Antioxidants, and vitamin E in particular, have been proposed to be beneficial against oxidative stress caused by heavy exercise, and while there are reports indicating benefit, the literature is quite divergent [13,19,25]. Vitamin E affects the immune system [15,17], and improves resistance to viral and bacterial infections in animals [5,6,17,27]. Under the assumption that physical activity causes oxidative stress which may harm the immune system, vitamin E could protect against these effects and thereby might influence the risk of infections.

The purpose of the present study was to determine whether moderate physical activity at work or during leisure time reduces the risk of pneumonia in middle-aged males, and whether long-term vitamin E or β-carotene supplementation affects the risk of pneumonia in physically active people.

Materials and Methods

Subjects

The design and methods of the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study examining the effects of vitamin E (α-tocopherol, AT, 50 mg/day) and β-carotene (BC, 20 mg/day) on the incidence of lung cancer and other cancers have been described in detail elsewhere [28, 29]. To be eligible, male participants aged 50–69 years had to smoke ≥ 5 cigarettes per day at entry, and those enrolled in the trial (n = 29 133) were randomized to one of four intervention groups and administered placebo, AT, BC, or AT + BC, using a 2 × 2 factorial design. Compared to baseline levels, supplementation increased the serum level of α-tocopherol by 50%, whereas serum β-carotene increased 15-fold [29]. The intervention continued for 5 to 8 years until April 1993. The trial was approved by the review boards of the participating institutions and all participants gave written informed consent.

For the present analysis, we excluded participants not gainfully employed at study entry (n = 12 321), because this is a highly heterogeneous group comprised of age- and health-related retirees, and others unemployed for various reasons for which data were not available. We also excluded participants with missing data on physical activity at work (n = 8), resulting in 16 804 participants working at study entry.

Baseline characteristics

Before randomization at baseline, the men completed questionnaires on medical and smoking histories and general background characteristics. A detailed dietary history questionnaire was completed which provided data regarding daily alcohol and coffee consumption [22]. Dietary data were not available for 1038 participants out of the 16 804.

The baseline questionnaire on physical activity at work and at leisure was a modification of that used originally in the Gothenburg study focusing on cardiovascular diseases [24]. The questionnaire asked about physical activity at work during the previous 12 months with the following alternatives and examples being given: 1) very light job: mostly sitting and not walking much, such as work in an office at a desk, as a clocksmith, or radio technician; 2) light job: walking a modest amount but not carrying heavy objects, such as office work that needs walking, foreman, salesman, or light factory work; 3) moderate job: walking a lot and carrying or lifting objects or walking up stairs or uphill, such as a carpenter, caretaker of livestock, or moderate factory work; and 4) heavy job: heavy physical work that needs a substantial amount of lifting or carrying heavy objects, digging or shovelling, or chopping wood, such as forestry, heavy farm work, or heavy construction and factory work.

The intensity of average physical activity during leisure time over the previous 12 months was asked with the following alternatives: 1) light: reading, watching TV, listening radio, or going to movies, mostly activities that are not physically loading; 2) moderate: walking, fishing, hunting, or gardening quite regularly; and 3) heavy: actual physical exercises, such as jogging, skiing, swimming, gymnastics, court and field sports quite regularly.

Outcome and follow-up time

Because the kind of job and physical activity at leisure can change with time, in particular among participants aged 50–69 years, we limited the follow-up time to 3 years. The events for this study, the first hospital-treated pneumonia after randomization were ascertained from the National Hospital Discharge Register using the unique personal identification number for linkage (see details in [10]). Pneumonia cases recorded in the Hospital Discharge Register reflect clinically more severe cases of greater health and economic significance, whereas less severe cases of pneumonia treated as outpatients are not recorded in the Register. Because almost all of the ATBC Study participants lived at home, the pneumonia cases ascertained represent community-acquired pneumonia; medical records were not reviewed to rule out the few nosocomial infections. There were 133 new cases of pneumonia during the 3-year follow-up among the 16 804 participants.

Statistical methods

Follow-up time for each participant began from the day of randomization, and continued until the date of first hospital discharge for pneumonia, death, or the end of the 3-year follow-up was reached, whichever came first. There were a total of 50 062 person years of observation among the 16 804 participants. Use of the Hospital Discharge Register permitted information on pneumonia to be obtained in all study participants, irrespective of whether they continued in or had dropped out from the trial.

We evaluated the association between physical activity and the incidence of pneumonia using proportional hazards regression [10]. We calculated the relative risk (RR) and the 95 % confidence interval (95 % CI) using the SAS PROC PHREG program (release 8.1, SAS Institute, Inc., Cary, NC, USA). We adjusted the models for physical activity and pneumonia risk for age and the number of cigarettes smoked per day as continuous variables, and body mass index, duration of smoking, and alcohol and coffee consumption as categorized in [10] and Table 1; these variables had substantial associations with pneumonia risk in a previous analysis of the ATBC Study cohort [10]. Nelson-Aalen cumulative hazard functions were constructed using the STATA sts program (Release 8.0, Stata Corp, College Station, TX, USA).

We also used proportional hazards regression to evaluate the effects of vitamin E and β-carotene supplementation on pneumonia incidence. The 2 × 2 factorial design of the trial permitted the assessment of the effects of vitamin E and β-carotene independently after confirming no statistical interaction between the interventions. Thus, we compared one half of the trial participants administered vitamin E with the other half not receiving vitamin E (the no-vitamin E group). Similarly, we compared one half of the trial participants administered β-carotene with the other half not receiving β-carotene. No covariates were included in the models analyzing the effect of intervention, because the large treatment groups originated from randomization and were balanced (data not shown). As to supplementation, we carried out the analyses following the intention-to-treat principle. Two-tailed p values were used.

Results

The basic characteristics of the participants working at baseline are shown in Table 1. Although the age range of the ATBC Study participants covered 50–69 years, only 14 % of working participants were 60 years or older. Forty percent of the participants had a moderate or heavy job activity. Sixty percent carried out moderate or heavy physical activity at leisure, but only 6 % of the participants participated in heavy exercise during leisure. There was no correlation between the intensity of physical activity at leisure, and the intensity of physical activity on the job (Spearman r = –0.04). There were 133 cases of pneumonia during the 3 years follow-up, corresponding to a rate of 2.7 episodes per 1000 person years.

We restricted the examination of the relationship between physical activity and the risk of pneumonia to the no-vitamin E group, because vitamin E affected the risk of pneumonia (see below). Physical activity on the job had no association with the risk of pneumonia. Moderate exercise at leisure was associated with a 50 % higher risk of pneumonia compared with sedentary persons, yet the difference was not statistically significant (Table 2). Findings in the placebo arm (no-vitamin E/no-β-carotene) were similar, but the confidence intervals were wider (not shown). In a stratified analysis by baseline smoking (≤ 20 and > 20 cigarettes per day), the relationship between physical activity and pneumonia risk was similar in both groups (data not shown).

Vitamin E and β-carotene supplementation had no effect on pneumonia risk in participants with moderate or heavy job activity (Table 3). β-Carotene had no effect on pneumonia among participants who carried out moderate or heavy physical activity at leisure. In vitamin E supplemented participants carrying out moderate or heavy physical activity at leisure, however, the risk of pneumonia was 50% of that of participants who were not supplemented with vitamin E (p = 0.009) (Table 3 and Fig. 1). To assess the stability of this estimate of effect by vitamin E supplementation among the participants carrying out physical activity at leisure, we carried out explorative subgroup analyses within participants living in a city with >50 000 inhabitants (n = 29 pneumonia cases), and those living outside cities (n = 36), and within married (n = 48) and unmarried (n = 17) participants, and in participants with dietary vitamin E intake below (n = 37) and above (n = 25) median. The effect of vitamin E supplementation ranged between 40 % and 57 % indicating that the estimate is quite stable in these six subgroups (data not shown).

Discussion

As regards the hypothesis that physical activity affects resistance to infections, pneumonia is an interesting case as it is a fairly common serious infection. Nevertheless, the rate of pneumonia among the ATBC Study participants was 300 times lower than the rate of the common cold which we analyzed previously [9]. This low rate of pneumonia leads to the problem of low statistical power. We used a 3-year follow-up to catch more cases of pneumonia, but a longer follow-up period contributes to more participants changing their physical activity status, rendering the baseline information less accurate. Also, even though we had a large number of participants, we had to collapse physical activity groups in Table 3 to obtain more stable estimates for the effects of vitamin E and β-carotene supplementation, yet this makes the groups with high level physical activity heterogeneous. All our participants were middle-aged male smokers and this may limit the possibility of generalizing our findings. However, in our cohort the relationship between physical activity and the risk of pneumonia was not different in participants who smoked more or less.

It has been proposed that regular moderate physical activity enhances the immune function and increases resistance to infections compared with a sedentary lifestyle [16, 21,26,30]. This suggestion is based on an extensive series of immunological studies, yet the effects of physical activity on the immune system are not quite consistent. However, if the fundamental question is whether a moderate level exercise reduces the risk of infections, then laboratory measures of the immune system are only surrogate markers and they should be considered cautiously because there are quite a few examples when the effect on a surrogate end point diverges from the effect on a hard clinical outcome [1,2]. In the present study the risk of pneumonia was not reduced with an increase in physical activity, and in our previous analysis of the ATBC Study cohort, common cold risk had no association with physical activity [9]. A recent smaller cohort study reported a 20 % lower risk of common cold among subjects with moderate physical activity [14]. Such slight differences may result from residual confounding, but even if the difference is a real consequence of exercise, this would correspond to some 4 people carrying out exercise for 1 year to prevent 1 episode of the common cold which is quite a low cost-benefit ratio. Concluding from the findings on the common cold and pneumonia, it seems that the reported effects of moderate exercise on the immune system may have little clinical importance in the long

term. This divergence between the effects of exercise on the immune system and on clinical infections highlights the importance of being cautious with nonvalidated surrogate markers, and the importance of using clinically meaningful end points [1,2].

Our participants were mainly engaged in physical exercise secondary to other free time activities, and only 6 % of the participants carried out actual heavy exercise at leisure. Consequently, our study with older middle-aged persons cannot address the question whether highly intense sporting activities such as a marathon run, or strenuous competitive sports training, might increase the risk of pneumonia as implied by the latter part of the "J"-curve [16,21,26,30].

Studies with animals and humans have found evidence of oxidative stress caused by heavy physical activity, and these changes were diminished by antioxidants, in particular by vitamin E [13,19,25]. Furthermore, antioxidants vitamin E and β-carotene can improve the functions of the immune system [11,15,17]. We examined whether vitamin E or β-carotene supplementation might decrease the incidence of pneumonia in participants performing moderate or heavy physical activity at work, or in participants carrying out moderate or heavy exercise at leisure, under the assumption that oxidative stress could be increased under such conditions, and the immune system might be protected by antioxidant supplementation. In participants categorized as having a moderate or heavy job, vitamin E and β-carotene had no effect on the risk of pneumonia. In participants carrying out moderate or heavy exercise at leisure, β-carotene had no effect on the risk of pneumonia, but the vitamin E group had a 50 % lower risk of pneumonia compared with no-vitamin E group.

The divergent effect of vitamin E in participants with a moderate or heavy job, and in participants with moderate or heavy exercise at leisure, is noteworthy. Possibly this divergence arises from different degrees of adaptation to physical stress. The body adapts to physical stress arising from a regular workload. There is a substantial amount of experimental evidence indicating that the activities of antioxidant enzymes increase in response to exercise in both animals and humans [13,25]. In contrast, people do not similarly adapt to oxidative stress caused by sporadic leisure time exercise, and consequently, heavy leisure time exercise could generate severe episodic oxidative stress. This would explain the benefit of vitamin E supplementation in participants carrying out leisure time exercise.

Although a 50 % reduction in the risk of pneumonia is a substantial effect, this point estimate should be considered cautiously as it arises from subgroup analyses and

thereby might have arisen by chance, as vitamin E had no overall effect on pneumonia risk in the ATBC Study cohort [10]. Also, with a pneumonia rate of 3 episodes per 1000 person years, a reduction of the rate by half corresponds to 667 people needing vitamin E supplementation for 1 year to prevent 1 episode of community-onset pneumonia, which, after all, is usually cured quite rapidly by antibiotics and rarely leads to long-term or permanent sequelae. Furthermore, in the previous analysis we found no benefit from vitamin E for the common cold risk in ATBC Study participants carrying out heavy exercise at leisure [9], and in this respect our two analyses of different respiratory infections do not point in the same direction which also makes us cautious with the finding. In parallel to vitamin E, vitamin C is interesting since these two antioxidants interact [4,18], and vitamin C also affects the immune system [7]. It is noteworthy that vitamin C supplementation reduced the risk of pneumonia by 85 % ($p = 0.044$) in a randomized trial carried out with Marine recruits in a training camp in the USA [8, 23]; in the placebo group, the rate of pneumonia was 120 episodes per 1000 person years, i.e. 44 times higher than the pneumonia rate among the ATBC Study participants.

In conclusion, physical activity was not associated with the risk of pneumonia. β-Carotene supplementation had no effect on the incidence of pneumonia in physically active participants. Vitamin E supplementation reduced the risk of pneumonia in participants carrying out moderate or heavy exercise at leisure. Though no straight practical conclusions should be drawn from this subgroup finding, further studies are warranted among persons carrying out moderate or heavy exercise.

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Table 1. Baseline Characteristics of Working Participants, the ATBC Study

Characteristic	Number of participants [a)]
All subjects	16 804
Physical activity at work	
Very light	4 007
Light	5 304
Moderate	4 808
Heavy	2 685
Physical activity at leisure	
Light	7 227
Moderate	8 528
Heavy	1 042
Age (years)	
50-54	8 765
55-59	5 691
60-64	1 968
65-69	380
Cigarettes (per day)	
5-19	5 246
20-29	7 973
≥30	3 585
Duration of regular smoking (years)	
<32	5 838
32-42	9 405
≥43	1 523
Body mass index (kg/m^2)	
<20	411
20-24	6 046
25-29	7 838
≥30	2 503

[a)] Data were not available for leisure activity, years of smoking, and body mass index for n = 7; 38; and 6 participants, respectively.

Table 2. The Risk of Pneumonia by Physical Activity at Baseline, the ATBC Study: No-Vitamin E Group

Characteristic	No. of Subjects	Pneumonia		
		No. of Cases	Rate (per 1 000 person-years)	RR (95% CI) [a)]
Physical activity on job				
Very light	2 037	21	3.5	1.00 (ref.)
Light	2 640	22	2.8	0.78 (0.41-1.47)
Moderate	2 388	15	2.1	0.64 (0.32-1.28)
Heavy	1 312	13	3.3	0.98 (0.46-2.04)
Physical activity at leisure				
Light	3 627	28	2.6	1.00 (ref.)
Moderate	4 255	41	3.2	1.51 (0.90-2.53)
Heavy	492	2	1.4	0.66 (0.15-2.84)

[a)] Proportional hazards regression model; adjusted for age, body mass index, the number of cigarettes smoked per day, duration of smoking, coffee and alcohol consumption; the multivariate model is based on 65 pneumonia cases in 7 835 participants with no missing data on confounders. Physical activity on job and at leisure were analyzed together using the same statistical model.
RR, relative risk; CI, confidence interval.

Table 3. The Effect of Vitamin E and β-Carotene on the Risk of Pneumonia in Physically Active Participants, the ATBC Study

Physical activity group	No. of subjects	Intervention: Vitamin E — Pneumonia: No. of cases	Intervention: Vitamin E — Pneumonia: Rate (per 1 000 pyrs)	Intervention: No vitamin E — Pneumonia: No. of cases	Intervention: No vitamin E — Pneumonia: Rate (per 1 000 pyrs)	RR (95% CI) [a)]
Moderate or heavy job	7 493	37	3.3	28	2.6	1.29 (0.79-2.11)
Moderate or heavy exercise at leisure	9 570	22	1.5	43	3.0	0.50 (0.30-0.84)
		β-Carotene		No β-carotene		
Moderate or heavy job	7 493	37	3.3	28	2.5	1.32 (0.81-2.17)
Moderate or heavy exercise at leisure	9 570	37	2.6	28	1.9	1.35 (0.83-2.21)

[a)] Proportional hazards regression model comparing participants who received vitamin E with those who did not, and participants who received β-carotene with those who did not. No covariates were included in the model.
RR, relative risk; CI, confidence interval.

Figure 1. Vitamin E supplementation and the risk of pneumonia in ATBC participants with moderate or heavy leisure time physical activity. Nelson-Aalen cumulative hazard functions for vitamin E and no-vitamin E groups are presented.