

Cancer incidence in a cohort of Finnish male smokers

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A total of 29 133 male smokers, aged 50–69 years, were recruited into the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study in 1984–1988. The nationwide Finnish Cancer Registry (FCR) recorded 5944 incident cases of cancer in this cohort through the end of 1999. Compared with the FCR data of the entire Finnish male population of same age the standardized incidence ratio (SIR) of total cancer in the ATBC cohort was 1.55 [95% confidence interval (CI) 1.51–1.59]. There was a significant excess of established smoking-related malignancies, such as lung cancer (SIR 2.45, 95% CI 2.35–2.56), and cancers of the tongue, mouth, pharynx, larynx, oesophagus, pancreas, stomach, liver, urinary bladder and kidney. In addition to these sites, cancers of the prostate and colon were slightly more common in the ATBC cohort than in the total Finnish male population (SIR 1.10, 95% CI 1.04–1.18 and SIR 1.14, 95% CI 1.00–1.30, respectively). In conclusion, the risk of many cancers was significantly higher in the ATBC Study cohort compared with the total Finnish male population of

same age. In addition to the well known smoking-related cancers, cigarette smoking may increase slightly the risk of colon and prostate cancer, too. *European Journal of Cancer Prevention* 15:103–107 © 2006 Lippincott Williams & Wilkins.

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Introduction

Smokers suffer from many types of cancer. In 2002, a working group from the International Agency for Research on Cancer (IARC) concluded that tobacco is a potent multi-site carcinogen causing cancers of the lung, upper aero-digestive tract (oral cavity, nasal cavity and sinuses, pharynx, larynx, oesophagus), pancreas, stomach, liver, lower urinary tract (renal pelvis and bladder), kidney, and uterine cervix, as well as myeloid leukaemia (IARC, 2004). Although smoking has been consistently associated with colorectal adenomas (Giovannucci and Martinez 1996) the association for colorectal cancers remains unclear (Vineis *et al.*, 2004). The evidence concerning smoking and colorectal cancer indicates high risk associated with a long smoking history, including many decades (Potter 1999; Sturmer *et al.*, 2000). The increased risk among smokers may be causal or result from inadequate adjustment for potential confounders (Vineis *et al.*, 2004). Prostate cancer has not commonly been associated with smoking (Kuper *et al.*, 2002; Vineis *et al.*, 2004), but some studies suggest a weak positive association (Lotufo *et al.*, 2000; Giles *et al.*, 2001; Plaskon *et al.*, 2003).

The purpose of this study was to describe the cancer pattern in male smokers participating in the ATBC Study and to compare it with that of the entire Finnish male population of the same age. Special attention was paid to cancers with an a priori inconsistent but plausible

association with smoking, such as cancers of the colon, rectum and prostate.

Material and methods

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was a double-blind, placebo-controlled primary prevention trial that tested the effect of alpha-tocopherol and beta-carotene supplementation on lung (and other) cancer incidence (ATBC Group, 1994a, b). Participants who were middle aged (50–69 years) male smokers were randomly assigned to four supplementation groups: alpha-tocopherol (50 mg/day), beta-carotene (20 mg/day), both agents, or placebo. In all, 29 133 men were recruited into the trial between 1984 and 1988, and the trial ended in April 1993. At study entry, all men smoked at least five cigarettes per day (median 20 cigarettes/day) and they had smoked for a median of 36 years.

The primary source of information on incident cancer cases for the study participants was the population-based Finnish Cancer Registry (FCR), which provides almost 100% case coverage nationwide (Téppo *et al.*, 1994; Korhonen *et al.*, 2002). Follow-up for cancers through the files of the FCR was done using the unique personal identification number. Follow-up for cancers started from randomization and ended at death or on 31 December 1999, whichever occurred first. The vital status of the

study participants was updated from the Central Population Register at the end of follow-up.

The number of observed cancer cases and person-years at risk were calculated, by 5-year age groups, separately for four calendar periods (1984–1987, 1988–1991, 1992–1995 and 1996–1999). The expected number of cases for total cancer and for specific organ sites was calculated by multiplying the number of person-years in each age group by the corresponding average male cancer incidence in all of Finland during the calendar period of observation. To calculate the standardized incidence ratio (SIR), the observed number of cases was divided by the expected number. The 95% confidence intervals (CIs) were based on the assumption that the number of observed cases followed a Poisson distribution.

The ATBC study cohort was between 50 and 69 years of age at study entry. Therefore, the accumulated number of cancer cases and person-years remained relatively small in those aged 80 years or older, resulting in wide confidence intervals for SIRs in site-specific results.

The ATBC Study found that the incidence of lung cancer was significantly higher in those receiving beta-carotene supplementation compared to those not receiving beta-carotene (ATBC Group, 1994a, b). In addition, alpha-tocopherol supplementation was found to be protective for prostate cancer (Heinonen *et al.*, 1998). Because of this, the SIRs for lung cancer and prostate cancer were calculated both for the entire cohort and for the placebo group only in order to control for the effect of study supplementation.

Results

During follow-up of 305 045 person-years, the FCR identified 5944 cancers excluding non-melanoma skin cancer in the cohort while the expected number was 3843, representing an SIR of 1.55 (95% CI 1.51–1.59) (Table 1). In the placebo group the observed number of all cancers was 1481 while the expected number was 968 resulting in an SIR of 1.53 (95% CI 1.45–1.61). The age-group-specific SIRs were also similar in the placebo group compared to the entire cohort with statistically significant elevated risks in all age groups excluding the oldest (i.e., 80 years or more).

Smoking-related cancers

The SIR for lung cancer was significantly elevated in the ATBC Study cohort. During follow-up, 2014 lung cancer cases were observed compared to 822 expected (SIR 2.45, 95% CI 2.35–2.56) (Table 2). The SIR for lung cancer increased with increasing age, from 2.15 among those aged 50–59 years to 3.41 among those aged 80 years or more, and was significantly elevated in all age groups. The results in the placebo group were similar, with 478 observed cases compared to 207 expected ones (SIR 2.30, 95% CI 2.11–2.52).

The SIRs for most smoking-related cancers (tongue, mouth, pharynx, larynx, oesophagus, pancreas, stomach, liver, bladder and kidney) were also significantly elevated in the ATBC cohort (Table 2). However, leukaemia (all types combined) and cancers of the lip and the nasal cavity and sinuses, were not more common in the ATBC cohort than in the entire male population. The effect of age was most consistently seen in oesophageal and laryngeal cancers where the SIRs increased with increasing age (in oesophagus from 1.15 in those aged 50–59 years to 1.72 in those aged 70–79 years and in larynx from 2.63 in those aged 50–59 years to 3.30 in those aged 70–79 years).

Table 2 Site-specific standardized incidence ratios (SIRs) and their confidence intervals (CIs) for most cancers among the Alpha-Tocopherol Beta-Carotene Study cohort in 1984–1999 compared to the general male population of same age

Site	Observed	Expected	SIR	95% CI
Lip	56	51	1.10	0.84–1.43
Tongue	22	14	1.57	1.04–2.39
Mouth other	31	15	2.03	1.43–2.88
Pharynx	49	25	1.97	1.49–2.60
Oesophagus	66	49	1.34	1.05–1.71
Stomach	277	207	1.34	1.19–1.51
Liver	90	56	1.61	1.31–1.98
Pancreas	237	135	1.76	1.55–2.00
Nose, sinuses	11	8	1.39	0.77–2.52
Larynx	128	53	2.40	2.02–2.86
Lung	2014	822	2.45	2.35–2.56
Kidney	227	169	1.35	1.18–1.53
Bladder	414	234	1.77	1.60–1.95
Melanoma of the skin	74	89	0.83	0.66–1.04
Nervous system	92	85	1.08	0.88–1.33
Non-Hodgkin lymphoma	107	89	1.21	0.99–1.46
Myeloma	31	44	0.70	0.49–0.99
Leukaemia	72	71	1.01	0.80–1.27

Table 1 Accumulation of person-years, observed and expected numbers of cancer cases, standardized incidence ratios (SIRs) and their 95% confidence intervals (CIs) among the Alpha-Tocopherol Beta-Carotene Study cohort in 1984–1999

Age (years)	Person-years	Observed	Expected	SIR	95% CI
50–59	97 569	799	490	1.63	1.52–1.75
60–69	165 966	3453	2176	1.59	1.54–1.64
70–79	40 871	1651	1148	1.44	1.37–1.51
80+	637	41	29	1.39	1.02–1.89
Total	305 045	5944	3843	1.55	1.51–1.59

Colon and rectum

The incidence of colon cancer was modestly but significantly higher (SIR 1.14, 95% CI 1.00–1.30) in the ATBC Study cohort than in the total male population (Table 3). The SIR for rectum cancer was close to unity (Table 3).

Prostate

In the entire ATBC Study cohort there were 987 observed prostate cancer cases during follow-up while the expected number of cases was 894 (SIR 1.10, 95% CI 1.04–1.18) (Table 3). The SIR was elevated up to age 69 years after which it was close to unity. In the placebo group there were 270 observed cases against 225 expected ones and the incidence ratio was slightly higher than for the entire cohort (SIR 1.20, 95% CI 1.06–1.35).

Other cancers

Of cancers not considered to be associated with smoking, only multiple myeloma showed a significant inverse association with smoking, SIR 0.70, 95% CI 0.49–0.99 (Table 2). In addition, the incidence of non-Hodgkin lymphoma was marginally increased in the ATBC cohort compared with the total male population, SIR 1.21, 95% CI 0.99–1.46. There was no indication of any significant difference between the general population and the ATBC cohort for cancers of non-melanoma skin, eye, Hodgkin lymphoma, bone, endocrine glands, soft tissues, pleura, gall bladder and bile ducts, or small intestine (data not shown).

Discussion

We examined the association between smoking and cancer by comparing the cancer incidence of a cohort of male smokers with that of the total Finnish male population of same age. The ATBC Study cohort consisted of male smokers who had been smoking for a median of 36 years at the time of randomization. Even

though smoking among Finnish males had decreased consistently from the 1950s, around 30–40% of the adult male population still smoked in the 1980s and 1990s (Vartiainen *et al.*, 2000; Sulander *et al.*, 2004). Thus, the comparison group (total male population of same age) in this study included current smokers, former smokers and never smokers. The fact that the comparison group also included many smokers diluted the incidence ratios, a proxy for the association between smoking and cancer. Nevertheless, the incidence ratios of most of the established smoking-related cancers were significantly elevated in the ATBC Study cohort, indicating a strong association between smoking and cancer incidence. This elevated risk was also observed in the placebo group eliminating a major effect of the trial supplements on the results. Another possible explanation for the excess risk could be participation in a cancer prevention trial that included regular visits to a study centre and nurses during the active trial period, and possibly increased awareness or detection of cancer and other illnesses. This is unlikely, however, because a similar increase was not observed for cancers not considered to be associated with smoking.

Lung cancer and other established smoking-related cancers were significantly more common in the ATBC Study cohort than in the general male population of the same age. This finding is not surprising when the smoking history of the cohort is considered and it is in harmony with many earlier reports and reviews (Dreyer *et al.*, 1997; Vineis *et al.*, 2004).

We found no smoking-related association for leukaemia, however. Myeloid leukaemia has been associated with smoking (IARC, 2004) but in the present study all types of leukaemia were combined, possibly contributing to the missing association. We also did not observe higher SIRs for cancers of the nasal cavity or sinuses, in contrast to the IARC evaluation suggesting a smoking-related association

Table 3 Observed and expected numbers of cancer cases and standardized incidence ratios (SIRs) with their 95% confidence intervals (CIs) in the Alpha-Tocopherol Beta-Carotene Study in 1984–1999

Organ	Age (years)	Observed	Expected	SIR	95% CI
Colon	50–59	34	27	1.26	0.90–1.76
	60–69	125	110	1.14	0.96–1.36
	70–79	64	60	1.07	0.84–1.37
	80+	3	2	1.81	0.58–5.60
	All	226	198	1.14	1.00–1.30
Rectum	50–59	21	23	0.91	0.59–1.40
	60–69	95	95	1.002	0.82–1.23
	70–79	43	45	0.95	0.70–1.28
	80+	1	1	1.01	0.14–7.17
	All	160	164	0.97	0.83–1.14
Prostate	50–59	54	41	1.31	1.00–1.71
	60–69	558	488	1.14	1.05–1.24
	70–79	360	354	1.02	0.92–1.13
	80+	15	11	1.42	0.86–2.35
	All	987	894	1.10	1.04–1.18

for these tumours (IARC, 2004), but we observed only a small number of cases in these sites. The IARC evaluation stated that smoking causes cancer of the oral cavity (IARC, 2004). In our study the SIRs for tongue and mouth cancer were significantly elevated whereas the SIR for lip cancer was only slightly elevated with 56 observed cases and 51 expected ones.

Colorectal cancer has not been consistently associated with smoking but long-term smoking has been associated with adenomas, precursors of colon cancer (Giovannucci *et al.*, 1994; Giovannucci and Martinez 1996). It has been hypothesized that smoking is related to colorectal cancer after an induction period of 30–40 years (Giovannucci and Martinez 1996). We observed 226 cases of colon cancer in the cohort when the expected number was 198 (SIR 1.14, 95% CI 1.00–1.30). This higher relative incidence may be due to confounding by smoking-related lifestyle factors, such as high intake of alcohol and saturated fats, low intake of vegetables and fruits, or low physical activity levels. On the other hand, since the total male population also included many smokers, the SIR was most probably attenuated towards null. The observed number of rectal cancer cases was close to the expected number, which is in line with the inconsistent findings of earlier studies (IARC, 2004).

In the present study, prostate cancer was observed significantly more often among the ATBC Study cohort than in the general male population of the same age. The relative rate, however, was only 10% higher but the smokers of the total population diluted this relationship. The 32% decrease in the incidence of prostate cancer among recipients of alpha-tocopherol (Heinonen *et al.*, 1998) also probably reduced the incidence ratio, supported by the finding that in the placebo group the relative incidence for prostate cancer was 20% higher than in the total male population of same age. The IARC working group found no clear evidence of higher risk for prostate cancer among smokers (IARC, 2004). Of the more recent studies not included in the evaluation, the US Physicians' Health Study, a cohort of 22 071 men and an average of 12.5 years follow-up, found a positive association between past smoking and risk for prostate cancer compared to those who had never smoked (RR 1.14, 95% CI 1.00–1.30) (Lotufo *et al.*, 2000). The study did not find an association between current smoking and risk for prostate cancer, however. On the other hand, a population based case–control study from the US reported an increased risk among current smokers compared to non-smokers (OR 1.4, 95% CI 1.0–2.0) (Plaskon *et al.*, 2003). It seems that data on smoking and prostate cancer risk has been mixed but evidence supporting a moderate association is increasing. In the present study, the SIR for prostate cancer was elevated up to age 69 years but similar to the general male population in older ages. This may be a consequence of

competing causes of death, due to the very long smoking history among participants in the ATBC study. Thus, the participants had a high risk of dying from other smoking-related diseases before reaching the age when the risk for prostate cancer is at its highest. Partly it may also be due to the fact that risk factors other than smoking have an important role in prostate carcinogenesis in older ages.

In conclusion, the ATBC Study cohort consisting of male, long-term smokers, had more established smoking-related cancers than the total Finnish male population of the same age. Among the participants of the cohort, the incidence of colon and prostate cancer was also elevated compared to the total population. These associations were modest and could be due to confounding by other smoking-related lifestyle factors. On the other hand, the many smokers within the total population attenuated these associations. Since colorectal and prostate cancers are common, even a small promoting effect of smoking may have notable public health impact.

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