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Every tenth malignant solid tumor attributed to overweight and alcohol consumption: A population-based cohort study

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ABSTRACT

Background: Recent studies have shown that some four in ten cancers are attributable to a few key risk factors. The aim of this study was to estimate cohort-based population attributable fractions (PAFs) in Finland for potentially modifiable cancer risk factors.

Methods: Data from eight health studies including 253,953 subjects with 29,802 incident malignant solid tumors were analysed using Bayesian multivariate regression model with multiplicative risk factor effects. We estimated the effects of smoking, excess body weight, alcohol consumption, physical activity, parity and education on cancer incidence and related PAFs by cancer site, accounting for competing mortality.

Results: PAF for all cancer sites and exposures combined was 34% (95% credible interval 29%−39%) in men and 24% (19%−28%) in women. In men, 23% (21%−27%) and in women 8% (6%−9%) of all cancers were attributed to smoking. PAF related to excess body weight was 4% (2%−6%) in men and 5% (2%−7%) in women, to alcohol 7% (3%−10%) in men and 4% (0%−7%) in women, and to excess body weight and alcohol combined 10% (6%−15%) in men and 9% (4%−13%) in women.

Conclusion: Smoking was the most important factor contributing to cancer burden in Finnish men and women over the last 40 years. The contribution of excess body weight and alcohol consumption together outweighed the role of smoking in women. As the prevalence of overweight is expected to increase, more efficient public health measures supporting adherence to healthy weight are essential to reduce cancer burden.

1. Introduction

Recent evaluations of lifestyle and environmental factors have attributed four in ten cancer cases to key modifiable risk factors. In the UK, 39% of cancers in men were attributable to exposure to 11 known cancer risk factors and 37% of cancers in women were attributable to 14 risk factors in 2015 [1]. Similar proportions were reported also for the US, Australia and Canada [2–4]. Risk factor contributions to the overall

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burden of cancer in the Nordic countries, including Finland, were evaluated in the late 1990′s [5]. In the respective study, 38% of cancers in men, and 16% in women were attributed to ten risk factors.

It has been conclusively shown that smoking, overweight, alcohol consumption, and physical inactivity are among the most important contributors to cancer incidence [6–9]. Recent studies from the Nordic countries evaluated the roles of specific risk factors in the burden of cancer [10–13]. It was estimated that 19% of incident smoking-related cancers in the Nordic countries in 2016–2045 could be avoided if smoking was eliminated [12]. By totally eliminating overweight and obesity, almost 10% of body fatness-related cancers could be avoided during the mentioned period [10]. Correspondingly, 6% of the alcohol-related cancers could be avoided in the absence of alcohol consumption [11]. With total elimination of the deficit in physical activity in the year 2016, 0·9% of the cancers of the breast, colon and endometrium could be avoided in 2016–2045 [13].

Many earlier studies have relied on published exposure-cancer associations and have applied them to the estimation of the population attributable fractions (PAFs) with the prevalences of the exposures obtained from other data sources. This may lead to biased estimates due to several reasons that are easier to control for in cohort studies: the measurement and categorisation of risk factors may not be comparable, and simultaneous effects of multiple risk factors on cancer risk and on the competing risk of death are not accounted for [14].

In this study, we aimed to estimate prospective cohort-based fractions of cancer attributable to key risk factors in Finland. We utilised data on cancer incidences and their multivariate associations with six potentially modifiable risk factors observed in eight health studies over the last 40 years, with analyses also accounting for competing mortality.

2. Methods

2.1. Study design and data sources

The study utilised data from the Prospective Meta-Cohort Study of Cancer Burden in Finland (METCA project) that pooled seven population-based cross-sectional health studies conducted in Finland between 1972 and 2015 [15]: Finnish Mobile Clinic Health Examination Follow-up Study (FMCF), National FINRISK Study (comprising nine studies conducted every five years from 1972 to 2012), Mini-Finland Health Study (MFH), Health 2000 Survey (H2000), Helsinki Birth Cohort Study (HBCS), Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) and Regional Health and Well-being Study (ATH). ATH study consisted of two datasets, the first collected in 2010–2011 (ATH1) and the second in 2012–2015 (ATH2). Additionally, a cohort of the City of Helsinki employees (HHS) was included in the present study. Descriptions of the participating studies can be found in the appendix (pp 2–3). The overall data included 253,953 subjects aged 18 to 100 years at baseline.

The health studies were performed in line with the principles of the Declaration of Helsinki. All studies were conducted according to the Finnish legislation in effect at the time of the study. The study was approved by The Finnish Institute for Health and Welfare (Permits no. THL/1091/6.02.00/2015 and THL/679/6.02.00/2018), which include evaluation of informed consent of each participating study. Cancer data was obtained according to national legislation of secondary use of health and social data (Act on the Secondary Use of Health and Social Data, 552/2019 and Act on the National Institute for Health and Welfare, 668/2008).

2.2. Outcomes

Altogether, 29,802 malignant solid tumors (including non-malignant central and nervous system cancers tumors and excluding skin non-melanoma) were diagnosed in men and women (Table 1). The primary sites were categorised as follows: mouth and pharynx (ICD-10 codes C00–14), stomach (C16), colon and rectum (C18–20), liver (C22), pancreas (C25), lung and trachea (C33–34), breast (C50), cervix uteri (C53), corpus uteri (C54), ovary (C56, C57.1–4, C48.1–2 serous), prostate (C61), kidney (C64), bladder and urinary tract (C65–68, D09.0–1, D41.1–9), and melanoma of the skin (C43). In addition, the other malignant solid tumors were included as a separate group. Hematologic malignancies were not included, because their current classification (WHO) was not available for most of the cases diagnosed before year 2007. Information on cancers and deaths were obtained from the nationwide Finnish Cancer Registry [16] and the Population Registry, respectively, by utilizing the unique personal identity code, assigned to all citizens and permanent residents of Finland. The follow-up started from the date of the study participation and ended by any of the following events taking place as the first observed event: cancer, death or end of follow-up (end of 2013 or 2015 depending on the study).

2.3. Covariates

Tobacco smoking, body mass index (BMI), alcohol consumption, leisure time physical inactivity and nulliparity were considered as potentially modifiable risk factors of cancer. Also, education was included as a surrogate of unmeasured risk factors. The categorisation of these factors is described in the appendix (pp 4–6). For evaluation of PAF an optimal level of each risk factor was defined based on either the strong evidence presented in Word Cancer Report [17] or by the World Cancer Research Fund [9] or statistically significant effects observed in our data, and these optimal levels are shown in Table 2. Both former and current smoking increase the risk of many types of cancer [7], and even moderate consumption of alcohol is known to elevate the risk of certain cancers, such as breast and colorectal cancer [8]. As for body weight, BMI of 18·5–24·9 kg/m^2 is generally considered to indicate healthy weight. Excess body weight has been shown to increase e.g. the risk of cancers of the colorectum, endometrium and kidney, but its effect on breast cancer is complex and dependent on the age of excess weight and the age of breast cancer diagnosis [9]. Greater weight in adulthood increases the risk of postmenopausal breast cancer, whereas being overweight or obese as an adult before menopause decreases the risk of premenopausal breast cancer. Being overweight or obese in young adulthood (between the ages of about 18 and 30 years) decreases the risk of both pre- and postmenopausal breast cancer [9]. Regarding physical inactivity, there is strong evidence for it increasing the risk of at least eight different cancer types [17]. Nulliparity in women is known to increase the risk of breast, endometrial and ovarian cancer, and decrease the risk of cervical cancer [17].

2.4. Statistical analysis

In the spirit of Laaksonen et al. [18], we constructed a multiplicative Bayesian model with piecewise constant baseline hazard for cancer and death (appendix pp 7–8). We assumed proportional hazards between the risk factor categories except for the effect of BMI in breast cancer that was modelled with three age-dependent effects (1: age at follow-up <55 years, 2: age at follow-up ≥ 55 and age at study participation <50 years, 3: age at follow-up ≥ 55 and age at study participation ≥ 50 years). These age categorizations were used to account for different age-dependent effects of BMI on the risk of breast cancer. Based on the multivariate regression model, posterior means and 95% credible intervals (CI) of pooled incidence rate ratios (IRR, the mean value of the distribution of cohort-specific effects) and of the PAF accounting for censoring due to competing mortality are reported. The PAF related to a risk factor is defined as the proportion of cancers avoided, if the subjects shared the same cancer incidence and any-cause mortality as those subjects with the optimal level of the risk factor. Participants with missing covariates were included in the model as a separate category to increase population representativeness of the results. The R software environment (version 4.1.0) was used in the analyses where the Bayesian model was

Table 1
Number (N) and proportion (%, including and excluding ATBC study) of persons and number of cancer cases diagnosed during follow-up in men and women by cancer site and risk factor.

Risk factor	Value	N	%	%[g]	Mouth, pharynx (N[h]=381)	Stomach (1241)	Colon and rectum (2948)	Liver (425)	Pancreas (1308)	Lung, trachea (6470)	Prostate (6226)	Kidney (1065)	Bladder and urinary tract (1831)	Melanoma of the skin (723)	Breast (3203)	Cervix uteri (118)	Corpus uteri (697)	Ovary (430)	Other solid cancers (2736)
MEN																			
Smoking	Never	31864	25	32	48	85	245	41	91	47	1028	79	115	116	NA	NA	NA	NA	297
	Former[a]	34414	26	34	71	137	399	72	120	359	1312	124	245	152	NA	NA	NA	NA	378
	Current[a]	61669	47	32	119	672	1313	205	669	5545	3850	531	1262	97	NA	NA	NA	NA	533
	Missing	2058	2	2	3	8	10	3	4	20	36	8	8	5	NA	NA	NA	NA	15
BMI	< 25 kg/m^2	48685	37	37	89	353	664	87	317	2705	2214	225	587	123	NA	NA	NA	NA	462
	Overweight[b]	57439	44	44	107	410	938	146	416	2531	3048	350	783	189	NA	NA	NA	NA	548
	Obesity[b]	20405	16	16	38	128	343	82	142	683	885	159	245	51	NA	NA	NA	NA	178
	Missing	3476	3	3	7	11	22	6	9	52	79	8	15	7	NA	NA	NA	NA	35
Alcohol	None	15633	14	15	20	101	204	31	96	665	660	88	192	40	NA	NA	NA	NA	131
	Moderate[c]	72620	64	67	79	438	988	143	429	3041	3335	406	860	154	NA	NA	NA	NA	483
	Heavy[c]	19275	17	14	34	143	356	54	181	1207	988	100	269	26	NA	NA	NA	NA	122
	Missing	5857	5	5	4	52	71	15	35	308	235	30	63	10	NA	NA	NA	NA	24
Leisure time activity	Active	89155	69	72	156	593	1311	189	588	3624	4234	465	1063	294	NA	NA	NA	NA	838
	Inactive[d]	38067	29	26	78	298	637	123	288	2305	1927	268	548	67	NA	NA	NA	NA	360
	Missing	2783	2	3	7	11	19	9	8	42	65	9	19	9	NA	NA	NA	NA	25
Education	Low[e]	59761	46	46	109	462	855	139	394	3026	2844	352	733	140	NA	NA	NA	NA	586
	Middle[e]	37672	29	27	65	273	616	100	276	2027	1863	236	547	99	NA	NA	NA	NA	336
	High[e]	29288	23	24	56	150	476	78	205	869	1434	139	328	118	NA	NA	NA	NA	270
	Missing	3284	3	3	11	17	20	4	9	49	85	15	22	13	NA	NA	NA	NA	31
Total		130005	100	100	241	902	1967	321	884	5971	6226	742	1630	370	NA	NA	NA	NA	1223
WOMEN																			
Smoking	Never	74348	60	NA	79	244	713	71	295	152	NA	225	123	245	1981	73	523	304	1032
	Former[a]	24141	19	NA	18	32	100	14	32	64	NA	39	28	51	532	14	73	40	175
	Current[a]	22601	18	NA	43	61	153	17	85	274	NA	53	49	55	644	30	93	79	282
	Missing	2858	2	NA	0	2	15	2	12	9	NA	6	1	2	46	1	8	7	24
BMI	< 25 kg/m^2	56864	46	NA	65	116	361	36	152	247	NA	102	82	158	1552	53	253	185	408
	Overweight[b]	39587	32	NA	49	128	356	38	165	155	NA	120	71	124	1012	43	237	144	477
	Obesity[b]	22758	18	NA	26	87	238	27	94	83	NA	92	37	65	563	18	195	91	43
	Missing	4739	4	NA	0	8	26	3	13	14	NA	9	11	6	76	4	12	10	33
Alcohol	None	29098	27	NA	36	115	270	35	143	130	NA	99	54	77	632	27	179	115	599
	Moderate[c]	62159	58	NA	50	83	312	27	120	186	NA	89	66	148	1241	36	213	129	504
	Heavy[c]	10545	10	NA	10	11	52	5	17	37	NA	7	9	22	229	3	19	10	354
	Missing	4749	4	NA	2	5	19	1	15	10	NA	8	3	6	48	2	10	4	56
Leisure time activity	Active	85480	69	NA	88	204	624	61	255	300	NA	195	129	253	2226	68	446	283	943
	Inactive[d]	35055	28	NA	50	130	344	41	156	181	NA	119	71	96	926	47	235	135	530
	Missing	3413	3	NA	2	5	13	2	13	18	NA	9	1	4	51	3	16	12	40
Parity	Parous	47968	78	NA	96	253	668	79	305	353	NA	238	138	250	2182	96	483	311	1100
	Nulliparous[f]	12555	21	NA	30	54	172	14	58	59	NA	37	30	46	576	16	123	77	233
	Missing	633	1	NA	1	4	5	1	4	7	NA	4	0	2	15	0	5	3	22
Education	Low[e]	44103	36	NA	52	134	383	38	167	228	NA	146	74	104	1096	49	269	187	630
	Middle[e]	41480	33	NA	47	124	336	35	133	163	NA	90	74	144	1102	41	222	140	515
	High[e]	33824	27	NA	38	72	244	28	109	94	NA	75	51	102	926	26	191	85	325
	Missing	4541	4	NA	3	9	18	3	15	14	NA	12	2	3	79	2	15	18	43
Total		123948	100	NA	140	339	981	104	424	499	NA	323	201	353	3203	118	697	430	1513

NA = Not applicable
[a] Former: smoking previously, but quitting; current: smoking regularly or non-regularly at the time of study participation
[b] Overweight: ≥ 25 kg/m^2 and < 30 kg/m^2; obesity: ≥ 30 kg/m^2
[c] Moderate: < 14 drinks per week in men and < 7 drinks per week in women; heavy: ≥ 14 drinks per week in men and ≥ 7 drinks per week in women
[d] Inactive: reporting not having any physically burdening leisure time activities or hobbies
[e] Tertiles based on the years of education or ordered categories of education
[f] Nulliparous: reporting not having children
[g] ATBC study was excluded, because PAFs were derived without ATBC cohort of male smokers
[h] Number of cancers in men and women combined.
More detailed description of variable categorization is given in the appendix pp. 4–6.

Table 2
Optimal levels of risk factors by cancer site.

	Smoking	BMI	Alcohol	Physical activity	Parity	Education
Mouth, pharynx	never	< 25	none			
Stomach	never	< 25	none	active		high[a]
Colon and rectum	never	< 25	none	active	parous[a]	
Liver	never	< 25	none			
Pancreas	never	< 25				
Lung, trachea	never	≥ 25[d]				high[a]
Breast	never[a]	< 25 or ≥ 30[bc]	none	active	parous	low[a]
Prostate		< 25	none[a]			
Cervix uteri	never				nulliparous[c]	
Corpus uteri		< 25		active	parous	low[a]
Ovary	never	< 25			parous	
Kidney	never	< 25		active		
Bladder and urinary tract	never			active		
Melanoma of the skin				inactive[a]		low[a]
Other solid cancers	never	< 25	none	active		

[a] No strong evidence but significant effect of the risk factor in this study.
[b] BMI < 25 kg/m^2, if age at follow-up ≥ 55 and age at study participation ≥ 50, and BMI ≥ 30 kg/m^2 otherwise.
[c] Protective effects of high BMI in breast (premenopausal cancer, and if BMI was high in young adulthood, postmenopausal cancer) and nulliparity in cervical cancer were ignored in the total PAFs over all cancer sites and/or risk factors (Table 3).
[d] Protective effects of high BMI in lung cancer observed in this study were ignored in the lung cancer specific and the total PAFs (Table 3).

implemented in JAGS (version 4.3.0) [19] using R package rjags (version 4–13). All study cohorts were utilised for the estimation of the risk factor effects, but in the derivation of PAF, ATBC study of male smokers was excluded to avoid overweighting of the prevalence of smokers.

2.5. Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

3. Results

Data accumulated 3·3 million years of follow-up. Median follow-up times ranged from 2·1 years to 36·8 years between the individual studies, and in the pooled data, the median was 6·8 years. The prevalence of risk factors and the number of cancers by risk factor are shown in Table 1 for the pooled data (appendix pp 9–10 for study specific numbers). Smoking, overweight and alcohol consumption were more common among men than women. In the pooled data, 66% of men and 37% of women were former or current smokers, 60% of men and 50% of women were overweight or obese and 80% of men and 68% of women consumed alcohol (ATBC study of male smokers was excluded).

3.1. Incidence rate ratios

IRRs of the risk factors for men and women are shown in Fig. 1 (results with 95% CIs in the appendix pp 11–17). Among cancers with strong prior evidence on the causal effect of smoking (Table 2), current smoking significantly increased the risk of all cancers except for ovarian and colorectal cancers in women (Fig. 1). For body fatness-related cancers, excess body weight (overweight or obesity) significantly increased the risk of stomach (in women), colorectal, liver (in men), prostate, corpus uteri and kidney cancers. In addition, the protective effect of high BMI was found for premenopausal breast cancer. Nulliparity was found to significantly increase the risk of breast and corpus uteri cancers. For alcohol-related cancers, heavy alcohol consumption significantly increased the risk of cancers of mouth and pharynx in men and breast and colorectal cancer in women.

We found some significant exposure-cancer associations for which no strong prior evidence on causal association exist. Smoking increased the risk of breast cancer: the pooled IRR among former smokers was 1·17 (95% CI 1·04–1·31) and among current smokers 1·09 (0·98–1·20). Excess body weight was associated with a decreased the risk of lung cancer (0·77; 0·70–0·83 for overweight and 0·71; 0·61–0·82 for obesity in men, and 0·73; 0·54–0·93 and 0·71; 0·50–0·94 in women, respectively). The risk of prostate cancer was increased among moderate (1·14; 1·00–1·31) and heavy alcohol drinkers (1·21; 1·01–1·48). Leisure time physical inactivity decreased the risk of skin melanoma in men (0·71; 0·50–0·96). In women, nulliparity increased the risk of cancers of colon and rectum (1·34; 1·04–1·66).

3.2. Population attributable fractions

The PAF for all risk factors and cancer sites combined was 34% (29–39%) for men and 24% (19–28%) for women (Table 3). Several site-specific PAFs for all risk factors combined were significant for men, the largest being observed for the cancers of lung (92%; 89–94%), liver (50%; 22–71%) and skin melanoma (41%; 25–54%). For women, the largest PAFs for all risk factors combined were obtained for the cancers of lung (67%; 59–74%), corpus uteri (30%; 19–41%), and breast (28%; 19–36%) and skin melanoma (28%; 10–45%).

For men, 23% (21–27%) and for women 8% (6–9%) of all cancers considered were attributed to smoking. Site-specific PAF related to smoking was the largest for lung cancer for both men (89%; 86–92%) and women (59%; 54–65%). The other largest smoking-related PAFs were for bladder (38%; 27–48%) and liver cancer (23%; 1–43%) for men and cancers of mouth and pharynx (24%; 13–36%) and bladder (20%; 11–29%) for women.

The PAF for excess body weight for all sites combined was 4% (2–6%) for men and 5% (2–7%) for women. The largest site-specific PAFs were for liver (25%; 11–37%) and kidney cancer (19%; 9–29%) for men and for corpus uteri (20%; 12–28%) and kidney cancer (19%; 6–32%) for women.

PAF for alcohol consumption over all sites considered was 7% (3–10%) for men and 4% (0–7%) for women. For men, alcohol-related PAF for prostate cancer was significant (12%; 4–20%). For women, the largest site-specific alcohol-related PAFs were observed for colorectal (10%; −1–20%) and breast cancer (7%; −1–15%), although neither were statistically significant.

PAF related to leisure time physical activity was 1% (0–2%) for men and –1% (–2–1%) for women and significant for melanoma of the skin in men (25%; 8–41%). PAF related to nulliparity in women was 2% (1–2%) for all sites combined. The site-specific nulliparity-related PAFs were significant for corpus uteri 5% (1–8%), colon and rectum 4% (1–7%), and breast 2% (0–4%) cancers.

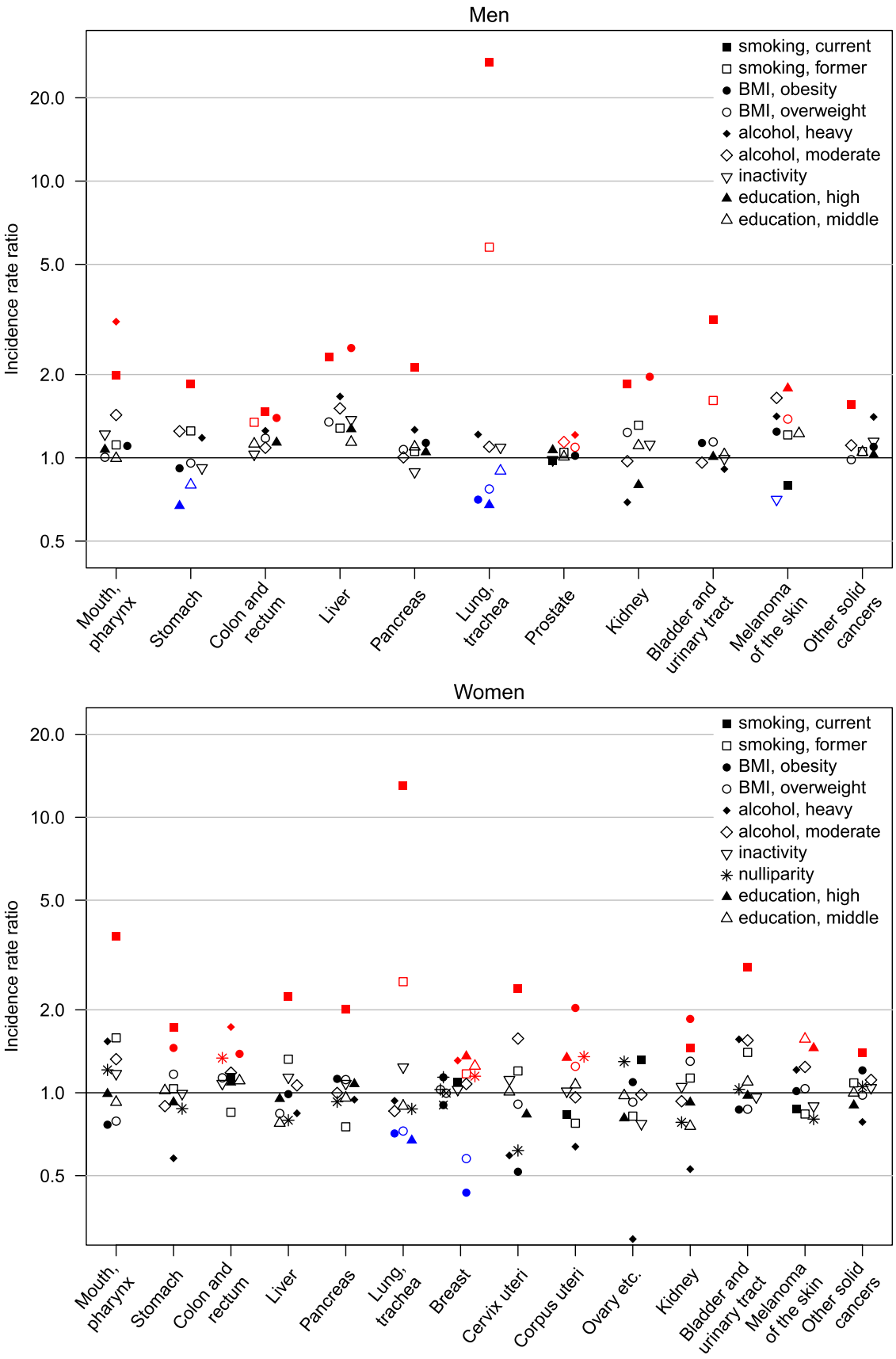

Fig. 1. Pooled incidence rate ratios for risk factors in men and women by cancer site. Red and blue letters indicate incidence rate ratios in which 95% credible interval does not cover unity. In breast cancer in women, incidence rate ratio for BMI was allowed to differ by age (denoted by circle: age at follow-up < 55, circled times: age at follow-up ≥ 55 and age at study participation < 50, circled plus: age at follow-up ≥ 55 and age at study participation ≥ 50).

Table 3
Population attributable fractions (%) with 95% credible intervals by risk factors and cancer sites in men and women.

	Smoking	BMI	Alcohol	Physical activity	Parity	Education	Total
MEN							
Mouth, pharynx	11 (−11, 29)	0 (−15, 16)	23 (−21, 55)	..	NA	..	33 (−7, 63)
Stomach	17 (−1, 32)	−4 (−15, 6)	18 (−8, 40)	−4 (−9, 2)	NA	16 (0, 31)	40 (13, 62)
Colon and rectum	10 (0, 20)	12 (5, 19)	4 (−13, 19)	−1 (−5, 2)	NA	..	28 (10, 43)
Liver	23 (1, 43)	25 (11, 37)	12 (−28, 45)	..	NA	..	50 (22, 71)
Pancreas	15 (0, 30)	4 (−6, 14)	..	..	NA	..	18 (2, 35)
Lung, trachea	89 (86, 92)	..	..	..	NA	20 (12, 26)	92 (89, 94)
Prostate	..	4 (0, 8)	12 (4, 20)	..	NA	..	15 (7, 23)
Kidney	19 (2, 34)	19 (9, 29)	..	2 (−4, 7)	NA	..	34 (18, 49)
Bladder and urinary tract	38 (27, 48)	..	..	−2 (−6, 2)	NA	..	37 (25, 47)
Melanoma of the skin	..	..	..	25 (8, 41)	NA	21 (10, 31)	41 (25, 54)
Other solid cancers	6 (−4, 16)	0 (−7, 7)	8 (−9, 23)	2 (−2, 6)	NA	..	14 (0, 27)
Total	23 (21, 27)	4 (2, 6)	7 (3, 10)	1 (0, 2)	NA	5 (4, 6)	34 (29, 39)
WOMEN							
Mouth, pharynx	24 (13, 36)	−16 (−37, 4)	8 (−25, 36)	..	..	..	22 (−13, 49)
Stomach	7 (1, 14)	11 (−3, 24)	−5 (−25, 11)	−4 (−13, 6)	..	7 (−15, 25)	8 (−30, 37)
Colon and rectum	−1 (−5, 3)	10 (3, 18)	10 (−1, 20)	−1 (−6, 5)	4 (1, 7)	..	23 (10, 36)
Liver	15 (3, 27)	−10 (−39, 17)	−15 (−63, 21)	..	..	..	−4 (−57, 35)
Pancreas	8 (2, 14)	5 (−7, 17)	..	..	..	..	13 (0, 25)
Lung, trachea	59 (54, 65)	..	..	..	..	20 (5, 34)	67 (59, 74)
Breast	4 (1, 7)	9[a] (2, 17)	7 (−1, 15)	−2 (−4, 1)	2 (0, 4)	15 (11, 19)	28[b] (19, 36)
Cervix uteri	18 (6, 31)	..	..	..	32 (−4, 63)	..	18[b] (6, 31)
Corpus uteri	..	20 (12, 28)	..	0 (−6, 5)	5 (1, 8)	9 (1, 18)	30 (18, 42)
Ovary	2 (−4, 8)	−1 (−13, 10)	..	..	4 (−1, 8)	..	3 (−11, 17)
Kidney	7 (0, 14)	19 (6, 32)	..	0 (−9, 9)	..	..	26 (10, 40)
Bladder and urinary tract	20 (11, 29)	..	..	−6 (−18, 5)	..	..	14 (0, 27)
Melanoma of the skin	..	..	..	8 (−10, 24)	..	22 (10, 34)	28 (10, 45)
Other solid cancers	6 (2, 9)	3 (−4, 9)	2 (−8, 12)	−1 (−5, 3)	..	..	9 (−1, 18)
Total	8 (6, 9)	5[b] (2, 7)	4 (0, 7)	−1 (−2, 1)	2[b] (1, 2)	8 (6, 10)	24[b] (19, 28)

Double middle dot denotes that population attributable fraction is set to zero according to Table 2. NA = Not applicable.

[a] Population attributable fraction for BMI in breast cancer was estimated by age and the estimates were

$$= \begin{cases} 4\ (1,\ 6) & \text{, if age at follow-up} < 55 \text{ (protective effect of high BMI)} \\ 4\ (-3,\ 10) & \text{, if age at follow-up} \geq 55 \text{ and age at study participation} < 50 \text{ (protective effect of high BMI)} \\ 2\ (-2,\ 5) & \text{, if age at follow-up} \geq 55 \text{ and age at study participation} \geq 50 \text{ (protective effect of BMI} < 25\ \mathrm{kg/m^2}) \end{cases}$$

[b] Protective effects of high BMI in breast (premenopausal cancer, and if BMI was high in young adulthood, postmenopausal cancer) and nulliparity in cervical cancer were ignored.

After smoking, the largest PAFs were thus for excess body weight and alcohol consumption. PAF for smoking and overweight/obesity together (25%; 21–30% in men and 12%; 10–15% in women) was close to that for smoking and alcohol consumption together (28%; 23–34% in men and 12%; 8–15% in women). Alcohol consumption and overweight/obesity together accounted for 10% (6–15%) of cancers in men and 9% (4–13%) in women.

4. Discussion

We found that 34% of the malignant solid tumors in men and 24% in women in Finland over the past 40 years were attributable to the key cancer risk factors. Smoking was the most important determinant of cancer burden, being responsible for 23% of the cancers in men and 8% in women. The respective PAFs for overweight/obesity were 4% and 5%, and for alcohol consumption 7% and 4%. Together, excess body weight

and alcohol consumption accounted for about 10% of the cancers.

Our overall PAF (34%) in men is broadly in line with the estimates for the UK (39%) [1], the US (43%) [2], Australia (34%) [3] and Canada (34%) [4]. The PAF for women (24%) was somewhat smaller than the previous estimates (37% for the UK, 42% for the US, 32% for Australia and 33% for Canada). The studies have included different sets of risk factors and cancers in the analyses, affecting the observed overall PAFs. Considering this, the reported overall PAFs are very concordant between different studies, suggesting a major role of few key factors included in all studies, such as smoking, excess body weight and alcohol consumption.

Our PAFs for smoking, overweight and alcohol consumption were larger than the earlier estimates of attributable fractions for Finland published in 1997 [5]. In men, our PAFs for smoking (23%) is higher than that for the UK (18%) but similar to that in US (24%). Our estimate for excess body weight for men (4%) is close to that for the UK (5%) and the US (5%), whereas our PAF for alcohol consumption for men (7%) is higher than those in the UK (3%) and US (5%). For women, our PAF for smoking (8%) was lower than what was estimated for the UK (12%) or the US (15%). Five percent of the cancers in women were attributed to excess body weight in our study, which is less than what was observed for the UK (8%) or the US (11%). Our PAF for alcohol consumption for women (4%) corresponds to the UK estimate (4%) but is slightly lower than the PAF observed for the US (6%).

The prevalence of risk factors changes over time and differs between countries, leading to differences in the reported PAFs. In Finland, the prevalence of smoking has decreased remarkably during the past decades, especially in men (from 36% in the late 1970′s to current 17%), while overweight or obesity has increased in both sexes (from 42% to 60% in men and from 37% to 50% in women) and alcohol consumption is much more common among women today than in the 1970′s (from 69% to 86% of women consuming alcohol) [20].

In the future, the role of excess body weight on cancer burden in Finland will likely become more important as the prevalence of obesity (BMI $\geq$30 kg/m^2) is projected to increase steadily [21]. In the age group 25–64 years, the projected prevalences in 2025 for both men and women are 24% (compared to around 20% in 2007). The trend is similar in many parts of the world as the number of people with obesity is expected to almost double between 2010 and 2030 [22].

We observed some significant exposure-cancer associations for which no strong/convincing evidence on causal association exist according to the World Cancer Report or the World Cancer Research Fund. The elevated risk of breast cancer among current smokers in our study is in line with the recently published meta-analysis [23]. In prostate cancer, we found an elevated risk associated with alcohol consumption. However, the prior evidence of this association is limited [24]. One potential confounder of the incidence of prostate cancer is the use of PSA testing which was not available in this study. Therefore, the estimate of PAF for alcohol in prostate cancer must be interpreted with due caution.

We did not find associations related to physical activity in the cancers of stomach, colorectal, breast, corpus uteri, kidney and bladder even though there is earlier convincing evidence on them. Our measure of physical activity included only leisure time physical activity, thus lacking information on work time activity. Also, our dichotomous physical inactivity variable measuring only leisure-time activity is probably not ideal for detecting beneficial effects of physical activity as we lack systematic information on the type, intensity and frequency of physical activity [15]. In skin melanoma, however, the risk was elevated among physically active men. Elevated risk of skin melanoma in high education group and physically active persons is likely to relate to ultraviolet radiation, because high socioeconomic status has been associated with sun holidays [25] and outdoor activities increase the risk of sunburn [26].

For lung cancer, the decreased incidence among subjects with excess body weight may be caused by residual confounding from smoking because smokers tend to have lower BMI than non-smokers [27]. A similar pattern has also been found for oral cavity cancer [28]. In the study by Bhaskaran et al. [28], confounding by amount of smoking was suggested to be the most likely explanation, because smoking data was only crudely categorised into former and current smokers as it is in our study. Reverse causation has also been suggested to have a role in the inverse association. Our earlier study [15] showed that the exclusion of the first two years of follow-up did not affect much the estimates of BMI in lung cancer, suggesting that reverse causation does not play a major role in this association. However, according to the study by Yu et al. [29], the inverse association between BMI and lung cancer may not be entirely due to smoking and reverse causation. As the interpretation of the association remains controversial, we did not evaluate PAF for BMI in lung cancer. In the cancers of mouth and pharynx, the optimal level for BMI was set according to previous evidence. We did not observe the association between BMI and cancers of the mouth and pharynx, which might be due to residual confounding of smoking or reverse causation. For smoking, the relative risk of cancers of mouth and pharynx, and consequently the corresponding PAF, was higher in women than men. The difference in IRR between men and women is concordant with some earlier findings [7].

Finnish population is relatively homogenous in terms of ethnicity, large majority being Caucasian, ethnic Finnish. The results of this study are generalisable to populations with somewhat similar demographic profile and very high human development index [30], among which the prevalence trends of known lifestyle factors also impacting cancer risk are likely to follow the same pattern. Regarding representativeness of the METCA data, in all studies except for HBCS (a birth cohort), ATBC (a cohort of male smokers) and HHS (employees' cohort) the inclusion of study subjects has been some variant of random selection from the Finnish population.

A major strength of our study is the large population-based prospective cohort data with harmonised risk factors and comprehensive follow-up for cancer and death based on the Population Information System and the Finnish Cancer Registry with 96% coverage for malignant solid tumors [16]. The study included cohorts with long follow-up, allowing long latency period from exposure to cancer, vital for reliable risk factor evaluation for many cancers. Because all information was derived from the participating studies, the observed rates of cancer incidence and competing mortality are valid for individuals with these specific risk factors values and competing mortality prior to cancer diagnosis as well as statistical random error were appropriately taken into account. Therefore, our PAF directly estimates the proportion of cancer cases that could have been avoided, if all individuals shared the same hazard of cancer and death as unexposed individuals. Ignoring mortality in the estimation of PAF has been shown to result in substantial bias [18] and may partly explain differences in PAFs reported in different studies.

A limitation of our study is that exposure information is derived from surveys of other non-communicable diseases. Therefore, we were unable to include certain known risk factors of cancers such as ultraviolet radiation and use of hormones. However, we included education in the analyses as a risk modifying factor, as it carries information on lifestyle factors which were not available but are known to be important in terms of cancer [31]. Also, education acts as a complementary surrogate for incompletely measured variables. Information on alcohol consumption was missing in the three earliest FINRISK studies (1972, 1977 and 1982) and in HBSC study. This decreases statistical power to observe significant effects for alcohol. It should also be noted that information on lifestyle factors was measured at the baseline of each survey after which the lifestyles may have changed. This results in information bias, which is likely to increase over follow-up time, and underestimation of the effects of the risk factors. PAF, on the other hand, estimates the proportion of cases avoided if the exposed individuals shared the same hazard of cancer and death as unexposed individuals. Therefore, if individuals in the unexposed group are exposed during the follow-up, PAF would also be underestimated. This might be the case especially with the

risk factors for which the prevalence has increased during the follow-up, such as for excess weight in men and women, and alcohol consumption in women [20]. The effect of information bias could be reduced by limiting the follow-up time. In our earlier study on the risk factors of lung and colorectal cancer, information bias did not have a notable effect on the results based on sensitivity analyses which restricted follow-up to the first 10 years after the baseline measurement [15]. In addition, the prevalence of exposures does not describe their current levels but their average distribution at time of the surveys. Our estimates for PAF ignored non-participants (who were invited but did not participate in any part of the survey), because their follow-up was not available. The participation rates in the studies showed a decreasing trend, ranging from 51% to 94% [15]. Non-participation has generally been found selective influencing the observed exposure prevalence. The PAF of the whole target population would likely be larger, because non-participants tend to have more unhealthy lifestyle than participants [32].

In conclusion, smoking was identified as the most important single lifestyle factor contributing to the cancer burden in Finnish men and women during the past 40 years. About 10% of cancers in both sexes in our study were attributable to excess body weight and alcohol consumption. In women, these two risk factors outweigh the role of smoking. Our results support the key role of avoiding smoking and alcohol consumption and maintaining healthy weight in the primary prevention of cancers. As the prevalence of overweight is expected to increase, more efficient public health measures supporting adherence to a healthy weight are essential to reduce the burden of cancer in the coming decades.

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CRediT authorship contribution statement

Karri Seppä: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft. **Sanna Heikkinen:** Conceptualization, Methodology, Data curation, Writing – original draft, Project administration. **Heidi Ryynänen:** Methodology, Data curation, Formal analysis, Writing – review & editing. **Demetrius Albanes:** Validation, Writing – review & editing. **Johan G. Eriksson:** Validation, Writing – review & editing. **Tommi Härkänen:** Validation, Writing – review & editing. **Pekka Jousilahti:** Validation, Writing – review & editing. **Paul Knekt:** Validation, Writing – review & editing. **Seppo Koskinen:** Validation, Writing – review & editing. **Satu Männistö:** Validation, Writing – review & editing. **Ossi Rahkonen:** Validation, Writing – review & editing. **Harri Rissanen:** Validation, Writing – review & editing. **Nea Malila**: Validation, Writing – review & editing. **Maarit Laaksonen:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision. **Janne Pitkäniemi:** Conceptualization, Methodology, Validation, Resources, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Permission to use survey and administrative health data, underlying our study, from various register keepers can be applied from Findata, the Social and Health Data Permit Authority. Requests to access these data can be submitted to the Findata: https://findata.fi/en/.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113502.

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