

# Proportion of cancer attributable to modifiable factors in the Netherlands in 2019: a secondary data analysis

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#### **ABSTRACT**

**Objective** To assess contributions of 22 risk factors (each related to life style, diet, reproduction, environment or infection) to the incidence of all cancer cases.

**Design** Secondary data analysis, reference year 2019. Independence of risk factors was assumed.

**Setting** The Netherlands, nationwide.

**Population** Dutch men and women, ages >30 years. **Main outcome measures** Population attributable fractions and numbers of newly diagnosed cancers by gender.

Results Of all newly diagnosed cancers, an estimated 34% (40 054 out of 119 728 cancers, excluding basal cell carcinoma of the skin) was attributable to the evaluated risk factors (35% in men, 32% in women). Among these factors, smoking was by far the largest contributor, accounting for 16% of all cancers (19 095 cases), followed by the combined impact of dietary factors (5%, 6 452 cases) and overweight and obesity (4%, 4995 cases). Limited data on basal and squamous cell carcinoma led to an underestimation of the burden of ultraviolet radiation. Conclusions A substantial proportion of cancer cases arises from potentially modifiable risk factors. Implementation of effective public health strategies to reduce exposures is crucial to alleviate the future burden of cancer.

#### INTRODUCTION

Worldwide, the burden of cancer is rising. <sup>1</sup> In the Netherlands, cancer is the main cause of disease burden with 16.5% of the total Dutch burden of disease. <sup>2</sup> Many exposures have been linked to the initiation of cancer, and many of these exposures are at least partly avoidable. Typically, not all cancer can be avoided, but estimates of the potential impact of modifiable risk factors are useful for strategic health planning and setting health priorities. <sup>3</sup>

In our prior study for the Netherlands in 2010, it was estimated that 30% of all newly diagnosed cancers, excluding non-melanoma skin cancer, was linked to lifestyle factors. However, at a population level, shifts in lifestyle behaviours occur over time. For example, in the past decades in the Netherlands, there has

#### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Many known causes of cancer are at least partly preventable.

#### WHAT THIS STUDY ADDS

⇒ In 2019, in the Netherlands, an estimated 34% (35% in men, 32% in women) of all cancers (40 054 out of 119728 cases, excluding basal cell carcinoma) were linked to modifiable risk factors. Lifestyle and diet accounted for 25% of all cancers, environmental exposures for 8%, infections for 2% and reproductive factors for 0.3%, with smoking as the leading contributor at 16%.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These estimates can support health planning and help focus efforts on cancer prevention.

been a steady decrease in smoking rates (from 35.3% in 1990 to 21.5% in 2019, according to Statistics Netherlands).<sup>5</sup> Changes in exposure levels are expected to influence the incidence of specific cancer types over time. Also, ongoing updates to evidence regarding the association between risk factors and cancer types as well as risk classifications of exposures contribute to fluctuations in estimates.<sup>67</sup>

The current study aims to provide up-to-date estimates of the proportions and quantities of newly diagnosed cancer cases attributable to potentially modifiable risk factors for the Netherlands in 2019. We assessed contributions of 22 risk factors (ie, cigarette smoking; alcohol intake; overweight and obesity; low consumption of fruit, vegetables, dietary fibre, dairy and coffee; consumption of red and processed meat; physical inactivity; ultraviolet and radon radiation; fine particulate matter (PM<sub>9.5</sub>, a proxy for outdoor air pollution<sup>67</sup>); infection with *Helicobacter pylori*, (H. pylori), hepatitis B virus (HBV), hepatitis C virus (HCV), HIV and human papillomavirus (HPV); oral contraceptive use;



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postmenopausal hormone replacement therapy (HRT); not breastfeeding) to 28 cancer types (table 1).

#### **METHODS**

### **Population**

The Netherlands is located in Northwestern Europe. According to Statistics Netherlands, by the end of 2019, the country had approximately 17.4 million inhabitants (average age 41 years). Total life expectancy at birth was 81.7 years (80.5 years in men, 83.6 years in women). The majority of the population (13.2 million) is of Dutch origin, while 24% (4.2 million) has a migrant background (5). Among migrants, approximately one-third originated from other European countries, while two-thirds came from outside Europe, primarily of Turkish, Surinamese or Moroccan descent. According to the Netherlands Cancer Registry (NKR), 45878 people (24788 men, 21090 women) died of cancer in 2019.

#### Identification of risk factors and cancer types

We used the reports of the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) and the International Agency for Research on Cancer (IARC) to identify factors that can potentially be modified to lower the risk of developing cancer. We only included combinations of risk factors and cancer types that were supported by convincing evidence (WCRF) or sufficient evidence (IARC) of a causal relationship, as acknowledged by international consensus. Based on this, a list of relevant cancer types was defined. Risk factors, cancer types or risk factor–cancer type combinations lacking this level of evidence, were purposefully excluded.

#### Modelling of population exposure

Population exposure was modelled using categorical distributions. For each risk factor, we defined two or three exposure levels, where the minimum-risk exposure group served as the reference group (eg, non-smokers) (table 1).<sup>3</sup> To ensure the practical value of our estimates, we used cut-off points for exposure levels that were in line with present public health statements and guidelines, issued by, among others, the Netherlands Nutrition Centre and the Health Council of the Netherlands.

#### Population attributable fractions and number of cases

Population attributable fractions (PAFs) were estimated, based on exposure prevalence and the associated relative risks (RRs). Each PAF defines the contribution of a specific risk factor to cancer on a population level. PAFs were calculated by using the standard formula for multicategory exposures<sup>3 9</sup>:

$$PAF=1-1/(p_0*RR_0+...+p_k*RR_k)$$

where  $P_0$  is the proportion or prevalence of the risk factor in the minimum-risk exposure group (ie, level 0, the reference category),  $RR_0$  is the RR in the minimum-risk exposure group (usually equal to one),  $p_k$  is the proportion or prevalence in the kth exposure level and

 $RR_k$  is the RRs comparing the risk in the kth exposure level with the minimum-risk exposure group. The effects of risk factors on cancer incidence may vary between men and women and across age groups. To account for these differences, PAF calculations were conducted stratified by gender and age class (ages 30–79 years in 10-year increments and 80 years and older). Due to lack of data, we were unable to stratify by other variables, such as sociodemographic and economic factors.

PAFs for ultraviolet radiation from sunlight and HPV were directly obtained from the existing sources. <sup>10 11</sup> The estimation of attributable cases involved multiplying the cumulative incidence of cancer in each gender and age class by the corresponding PAF for that demographic group. Incidental protective effects (oral contraceptives reduce the risk of endometrial cancer, colorectal cancer, ovarian cancer and liver cancer; alcohol intake, up to an exposure of approximately 2 glasses per day, lowers the risk of kidney cancer) were included in the calculation of the absolute numbers of attributable cases.

#### **Combining PAFs**

We aggregated PAFs across the strata of age groups, sexes and major risk factor groups (lifestyle, diet, environment, infections, female reproduction). To prevent overestimation during the merging of PAFs, we applied the formula introduced by Parkin<sup>12</sup>:

$$\label{eq:paf_combined} \text{PAF}_{\text{combined}} = 1 - (1 \text{-PAF}_1) * \dots * (1 \text{-PAF}_k).$$

Exposure to some risk factors increases the risk of certain cancer types, while this exposure decreases the risk of other cancer types. Use of oral contraceptives increases the risk of breast cancer and cervical cancer, while concurrently reducing the risk of uterine cancer, colorectal cancer, ovarian and fallopian tube cancer, and liver cancer. Alcohol intake, up to an exposure of approximately 2 glasses per day, lowers the risk of kidney cancer. We included the potential positive as well as the potential negative impacts on cancer incidence in our aggregation because we aimed to inform public health strategic planning in the first place.

#### **Exposure prevalences**

For all risk factors but cigarette smoking, a biological latency time of 10 years was assumed. Cancer incidence data from 2019 were linked to exposure data obtained as closely as possible to 2009. For cigarette smoking, exposure data from the year 2000 were used (ie, an assumed biological latency of 20 years). The year 2019 was selected as the reference year because in 2020, in response to the COVID-19 pandemic, cancer diagnosis was delayed, which temporarily reduced the overall cancer incidence in the Netherlands. At that time, data for the years 2021 and 2022 were not yet available. Gender-specific and age-specific exposure prevalences were gathered from Statistics Netherlands and published data from representative population surveys and laboratory research.



Reference			
(minimum-risk exposure level)	Exposure level 1	Exposure level 2	Associated cancer types
Never smoked	Ex-smoker	Smokes (at least occasionally)	Acute myeloid leukaemia; pancreas; cervix; urinary bladder; colorectum; ovary; head and neck; lung; liver; stomach; kidney; oesophagus
Non-drinker or ≤1 glass per day	Moderate drinkers (>1 to <4 glasses per day)	Heavy drinkers (≥4 glasses per day)	Breast (male and female premenopausal and postmenopausal); colorectum; oral cavity, pharynx, larynx; liver; stomach; kidney*; oesophagus (squamous cell carcinoma only)
Normal weight—BMI of 18.5–25 kg/m²	Moderate overweight—BMI of 25–30 kg/m <sup>2</sup>		Pancreas; corpus uteri; breast (male and female pre- and postmenopausal); colorectum; ovary; oral cavity, pharynx, larynx; liver; gallbladder; stomach (cardia only); kidney; prostate; oesophagus (adenocarcinoma only)
Active, meets physical activity guidelines (≥150 min/week moderate-intensity aerobic activity) <sup>21</sup>	Inactive, does not meet physical activity guidelines (<150 min/week)	-	Corpus uteri; breast (male and female pre- and postmenopausal); colorectum
<10 g per day	≥ 10-70 g per day	≥ 70 g per day	Colorectum
No processed meat	1-50g per day	≥ 50 g per day	Colorectum
High intake	Low intake	-	Lung, oral cavity, pharynx, larynx
High intake	Low intake	_	Lung, oral cavity, pharynx, larynx
Women minimum 30 g per day, men minimum 40 g per day	-	Women<15g per day, men<20g per day	Colorectum
Minimum 300 g per day (≥2 servings)	150-300 g per day (1 to 2 servings)	Less than 150 g per day (< 1 serving)	Colorectum
Minimum 50 g per day	No coffee or<50 g per day	_	Corpus uteri; liver
Ever during lifespan	Never during lifespan	_	Breast (hormone receptor negative only)
Never used during lifespan	Ever used during lifespan	-	Cervix; corpus uteri; breast colorectum; ovary; liver§
Never during lifespan	Ever during lifespan	_	Corpus uteri; breast; ovary
	Non-drinker or ≤1 glass per day  Normal weight—BMI of 18.5–25 kg/m²  Active, meets physical activity guidelines (≥150 min/week moderate-intensity aerobic activity)²¹¹  <10 g per day  No processed meat  High intake  Women minimum 30 g per day, men minimum 40 g per day  Minimum 300 g per day (≥2 servings)  Minimum 50 g per day  Ever during lifespan  Never used during lifespan	(minimum-risk exposure level)       Exposure level 1         Never smoked       Ex-smoker         Non-drinker or ≤1 glass per day       Moderate drinkers (>1 to <4 glasses per day)	(minimum-risk exposure level)       Exposure level 1       Exposure level 2         Never smoked       Ex-smoker       Smokes (at least occasionally)         Non-drinker or ≤1 glass per day       Moderate drinkers (>1 to <4 glasses per day)

Continued



Tahla 1	Continued

	Reference (minimum-risk exposure			
Risk factor	level)	Exposure level 1	Exposure level 2	Associated cancer types
Outdoor fine particulate matter (PM <sub>2.5</sub> )	Average annual concentration<15.01 µg/m <sup>3</sup>	Average annual concentration of at least 15.01 µg/m³¶	_	Lung
Ultraviolet radiation from		least 13.01 µg/III		Lung
sunlight	Low exposure	High exposure	_	Melanoma of the skin
Radon	Average annual effective radiation dose<15.6 Bq/m³	Average annual effective radiation dose at least 15.6 Bq/m <sup>3</sup> **	_	Lung
Infections				
H. pylori	Anti-H. pylori IgG negative	Anti-H. pylori IgG positive	_	Stomach
HBV	HBsAg negative	HBsAg positive	_	Liver
HCV	Anti-HCV negative	Anti-HCV positive	_	Liver; non-Hodgkin's lymphoma
HIV	Seronegative	Seropositive	_	Anus; Kaposi sarcoma; cervix; Hodgkin lymphoma; non-Hodgkin's lymphoma
HPV	HPV negative	HPV positive		Cervix; vagina; vulva; penis; oropharynx

<sup>\*</sup>Alcohol intake, up to an exposure of approximately 2 glasses per day, lowers the risk of kidney cancer.67

#### **Relative risks**

RRs for combinations of cancer types and risk factors were identified through systematic literature searches in PubMed. RRs were considered usable if they aligned with available exposure data in terms of exposure categories and units of measurement. Only RRs that were adjusted for multiple confounders (eg, other exposures) were selected. In cases where an RR was provided for the presence of an exposure factor, and an RR for the absence of that exposure was required, the RR for the absence was calculated by taking the reciprocal of the original RR (1/ RR).

Preferential consideration was given to recent, high-quality meta-analyses based on prospective studies or large-scale (pooled) individual data cohort studies. Within meta-analyses, priority was given to RRs based on European data when subanalyses were available. Gender-specific RRs and RRs per unit of exposure were selected whenever possible (eg, per 10 g of alcohol per day). RRs per unit of exposure were converted into RRs per exposure group, based on the average exposure level or the mid-level exposure in that group. To prevent overestimation of PAFs, RRs for open-ended exposure levels (eg, heavy drinkers, ≥4 units of alcohol per day) were based

on the lowest possible level of exposure in that group (ie, 4 units per day). For female breast and uterus cancer, life stage-specific (premenopausal or postmenopausal) RRs were used. Additionally, histological subtype-specific RRs were used whenever relevant (eg, for oesophageal cancer, where obesity is only associated with adenocarcinomas).

#### **Cancer incidence**

Data on newly diagnosed invasive cancer cases (excluding basal cell carcinoma of the skin) for the entire Dutch population by gender and age group (ages 30–79 years in 10-year increments and 80 years and older), for the year 2019 (cumulative incidence), were obtained from the Netherlands Cancer Registry (NCR). The NCR provided customised figures for national cumulative incidences of adenocarcinoma and squamous cell carcinoma of the oesophagus as well as hormone receptor-negative female breast cancer.

Detailed information, by age and gender, on the exposure prevalences, the RRs and the incident numbers of cancer cases considered in this analysis is provided in online supplemental tables.

<sup>†</sup>Physical activity, fruits, vegetables, dietary fibre, coffee and dairy intake have a risk-reducing effect in men and women.

<sup>‡</sup>Breastfeeding lowers the risk of cancer in women.

<sup>§</sup>Oral contraceptives reduce the risk of endometrial cancer, colorectal cancer, ovarian cancer and liver cancer.

<sup>¶</sup>The annual average exposure in the Netherlands around 2010 was 15.01 μg/m<sup>3</sup>.<sup>22</sup>

<sup>\*\*</sup>The average effective radiation dose in Dutch homes around 2010 was 15.6 Bq/m<sup>3</sup>.23

BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; PM2,5, outdoor fine particulate matter.



**Table 2** Estimated number of incident cancer cases, and percentages of all cancer (excluding basal cell carcinoma of the skin), attributable to the risk factors\* (2019, the Netherlands)

	Women		Men		Persons*	
Risk factor	Attributable cases	PAF† (%)	Atributtable cases	PAF† (%)	Attributable cases	PAF† (%)
All evaluated risk factors						
taken together	18047	31.9	21 927	34.7	40 054	33.5
Lifestyle and poor diet	12708	22.5	17571	27.8	30321	25.3
► Cigarette smoking	7388	13.1	11 708	18.5	19095	15.9
► Poor diet	2402	4.2	4037	6.4	6452	5.4
Fruit	834	1.5	1111	1.8	1946	1.6
Vegetables	516	0.9	1112	1.8	1628	1.4
Dietary fibre	426	0.8	1043	1.7	1469	1.2
Dairy	128	0.2	148	0.2	276	0.2
Coffee	5	0.0	3	0.0	8	0.0
Processed meat	416	0.7	561	0.9	977	0.8
Red meat	208	0.4	369	0.6	577	0.5
► Overweight and obesity	2052	3.6	2943	4.7	4995	4.2
► Physical inactivity	1556	2.8	672	1.1	2228	1.9
► Alcohol intake	658	1.2	481	0.8	1140	1.0
Environment	4386	7.8	4676	7.4	9063	7.6
<ul><li>Ultraviolet exposure from sunlight</li></ul>	3162	5.6	3213	5.1	6374	5.3
<ul> <li>Outdoor fine particulate matter (PM<sub>2.5</sub>)</li> </ul>	1161	2.1	1387	2.2	2548	2.1
► Radon	78	0.1	93	0.1	171	0.1
Infections	1567	2.8	1000	1.6	2567	2.1
► HPV	1221	2.2	401	0.6	1622	1.4
► H. pylori	290	0.5	427	0.7	717	0.6
► HIV	10	0.0	78	0.1	89	0.1
► HCV	28	0.0	56	0.1	83	0.1
► HBV	22	0.0	45	0.1	67	0.1
Reproduction	317	0.6	0	0.0	317	0.3
► Not breastfeeding	196	0.3	0	0.0	196	0.2
► Oral contraceptives	83	0.1	0	0.0	83	0.1
► Perimenopausal HRT	40	0.1	0	0.0	40	0.0

\*Due to rounding differences and because (underlying) numbers were estimated separately (based on proportions and relative risks), the total of numbers and percentages may not always add up perfectly across risk factors and from men and women to overall numbers. †Population attributable fraction, estimated percentage of new diagnoses attributed to the risk factor, compared with the total number of new diagnoses. In the reference year 2019, a total of 119728 individuals (63166 men and 56562 women) received a cancer diagnosis. This includes the total of all newly diagnosed cancers, excluding basal cell carcinoma of the skin (a common form of skin cancer that is almost never life-threatening). Basal cell carcinoma of the skin is not included in the total. HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; HRT, hormone replacement therapy; PAF, population attributable fractions; PM<sub>25</sub>, outdoor fine particulate matter.

#### **RESULTS**

In the Netherlands in 2019, there were 119728 new diagnoses of cancer, with 63166 cases among men and 56562 among women, excluding basal cell carcinoma of the skin (12). Exposure to the assessed risk factors accounted for 34% of these cancer cases (40054 out of 119,729). This percentage was higher for men (35%) than for women (32%). Table 2 shows the percentages and numbers of

cases associated with each evaluated risk factor, both independently and when combined with other factors.

#### Lifestyle and diet

An estimated 25% of all cancers (30321 out of 119728 cancers, 17571 in men (28%) and 12 708 (23%) in women) were attributed to the combination of the assessed lifestyle and dietary factors (table 2). This



combined influence specifically contributed to lung cancer (77% of all lung cancers, amounting to  $10\,981$  cases), oesophageal squamous cell carcinoma (70%, 465 cases), head and neck cancer (68%, 2141 cases) and liver cancer (56%, 600 cases).

Cigarette smoking accounted for the largest proportion and number of cases among all assessed risk factors  $(16\%, 19\,095\,\text{cases})$ , with  $11\,708\,(19\%)$  in men and  $7388\,(13\%)$  in women). We estimated that cigarette smoking caused 72% of all lung cancers  $(10\,261\,\text{cases})$ , 68% of all head and neck cancer  $(2141\,\text{cases})$  and 65% of all oesophageal squamous cell carcinoma  $(432\,\text{cases})$ .

The second-largest contribution from the assessed risk factors was from a poor diet, accounting for 5% of all cancers (6452 cases, with 4037 (6%) in men and 2402 (4%) in women). Low fruits (1.6% s) and vegetables (1.4%) intakes made the largest contributions, followed by a low dietary fibre intake (1.2%), processed (0.8%) and red meat consumption (0.5%), and low dairy intake (0.2%). Dietary factors mainly contributed to oral, pharyngeal and laryngeal cancer (35% of all oral, pharyngeal and laryngeal cancers, 896 cases) and colorectal cancer (23%, 3024 cases).

Overweight and obesity accounted for 4% of all newly diagnosed cancers (4995 cases, with 2,943 (5%) in men and 2052 (4%) in women), notably impacting liver cancer (37% of all newly diagnosed primary liver cancers, 395 cases), uterine cancer (32%, 682 cases) and adenocarcinoma of the oesophagus (32%, 543 cases).

Physical inactivity accounted for 2% of all cases (2228 cases, with 672 (1%) in men and 1556 (3%) in women), primarily affecting colorectal cancer (10% of all colorectal cancers, 1264 cases), uterine cancer (10%, 202 cases) and female breast cancer (5%, 763 cases).

Alcohol intake accounted for an estimated 1% of all cancers (1140 cases, with 481 (1%) in men and 658 (1%) in women), with notable impacts on mouth, pharynx or larynx cancer (18% of all mouth, pharynx or larynx cancers, 459 cases), and oesophageal squamous cell carcinoma (14%, 95 cases).

#### **Environment**

Ultraviolet radiation accounted for the third-largest percentage (5% of all cancers, excluding basal cell carcinoma) and the third-largest number of cases (6374 melanomas of the skin) among all assessed risk factors (table 2).  $PM_{2.5}$  and radon exposure accounted for lower percentages and numbers of cases, specifically 2.1% (2584 cases) and 0.1% (171 cases) of all cancers, respectively.

#### Infections

HPV contributed with the largest percentage and numbers of cases (1%, 1622 cases), followed by H. pylori (0.6%, 717 cases). Lower percentages and numbers of cases were attributed to HIV, HCV and HBV infections (0.1% for all, and fewer than 90 cases per infection).

#### **Female reproduction**

The largest contribution came from not breastfeeding (0.2%, 196 cases) (table 2). Female reproductive factors primarily contributed to breast cancer and cervical cancer. Oral contraceptives also have a protective effect, reducing the number of cases of uterine cancer (-617), colorectal cancer (-602), ovarian and fallopian tube cancer (-235) and liver cancer (-21).

#### DISCUSSION

For the Netherlands in 2019, we found that 34% of all cancers (40054 cases out of 119728, excluding basal cell carcinoma of the skin) was attributable to modifiable risk factors. This percentage was slightly higher for men (35%) than for women (32%). An estimated 25% of all cancers (30321 cases) were attributable to suboptimal lifestyle and poor diet, 8% (9063 cases) to environmental exposures (ultraviolet radiation from sunlight, PM<sub>9.5</sub> and radon), 2% (2567 cases) to cancer-related infections (HPV, H. pylori, HIV, HCV and HBV), and 0.3% (317) cases) to female reproduction factors (not breastfeeding, oral contraceptives and perimenopausal HRT). Cigarette smoking emerged as the primary contributor, accounting for an estimated 16% of all cancers (19095 cases), followed by a suboptimal diet (5%, 6452 cases), ultraviolet exposure from sunlight (5%, 6374 melanomas of the skin), and overweight and obesity (4%, 4995 cases). The impact of diet was mainly through low intakes of fruits (2% of all cancers, 1946 cases), vegetables (1%, 1628 cases) and dietary fibre (1%, 1469 cases).

#### **Strengths and limitations**

An important strength of our study lies in the quality of the underlying data. Exposure estimates were derived from nationally representative population surveys and laboratory research. RRs were obtained from high-quality meta-analyses of prospective studies.

Calculations were stratified by age and gender, and only RRs that were adjusted for multiple confounders were picked. Despite efforts to control confounding, complete control of confounding remains elusive due to the complexity of combining many exposures and RRs. Stratification by sociodemographic and socioeconomic factors could have enhanced the study; however, this was not possible due to a lack of available data. Potential synergistic effects of the combination of risk factors may have led, for some risk factors, to an underestimation of the PAFs and the number of cases. For example, cigarette smoking and alcohol drinking alone have a relatively small effect on oesophageal cancer risk, while in combination, there is a synergistically larger effect. <sup>13</sup>

A biological latency time of 10 years (20 years for cigarette smoking) was assumed. This time lag may be considered relatively short for most evaluated risk factors, but this assumption aligns with other studies, thus enabling international comparisons. 14–17



Limitations of the study included the absence of adequate data on ultraviolet radiation. Although the relationship with skin melanoma could still be considered, as Arnold and colleagues<sup>10</sup> estimated a PAF from the historical incidence of melanoma, our study did not include the most common skin cancers, namely basal cell carcinoma and squamous cell carcinoma. This exclusion was also due to a lack of data on the incidence of basal cell carcinoma and the RR for both basal cell carcinoma and squamous cell carcinoma. Consequently, our estimates regarding the impact of ultraviolet radiation are considered a serious underestimation. If we conservatively estimate the proportion of all newly diagnosed cases of these skin cancers caused by ultraviolet radiation at 85%, <sup>10</sup> the PAF for ultraviolet radiation would be six to seven times higher than the PAF estimated in this study (5.3), making ultraviolet radiation the most significant cause of cancer in the Netherlands, surpassing even cigarette smoking.

The impacts of some avoidable, cancer-causing exposures (such as secondhand smoke and indoor air pollution) remained unstudied, mainly because of lack of adequate exposure data. For other factors, like pesticides and most PFAS, the epidemiological evidence linking them to cancer was inconclusive, but this might change in the future.<sup>7</sup>

#### **Comparisons**

A similar study, focusing on lifestyle and dietary factors, was previously conducted by our team for the reference year 2010.4 The overall pattern remained consistent across the years: smoking remained the leading cause of cancer, followed by an unhealthy diet. However, since 2010, PAFs for smoking, overweight, alcohol, low intake of fruit, vegetables, fibre and dairy, high intake of red and processed meat and physical inactivity have all declined. Meanwhile, cancer incidence in the Netherlands rose: from over 98 000 cases in 2010 to nearly 120 000 in 2019. Population ageing and improved detection technologies may in part explain the drop in PAFs. Public health improvements may also have contributed: smoking rates declined (from 27% in 2010 to 20% in 2019) and physical activity rates increased. In 2010, 43% of the population >18 years met the physical activity guideline of 150 min per week; by 2019, this had increased to 49%. 5 18

Absolute cancer cases linked to smoking and inactivity were similar between 2010 and 2019. Cases attributable to poor diet and alcohol declined (from 9521 to 6452 and from 2868 to 1140, respectively); some cancers previously linked to low fruit and vegetable intake were later reassessed, and the Dutch alcohol threshold was revised from zero to one glass per day. Only cases attributable to overweight increased (from 3629 in 2010 to 4995 in 2019), mirroring rising obesity prevalence.

Comparisons with other countries, including the United Kingdom (UK), Denmark, the USA and Finland revealed broadly consistent trends, with cigarette smoking having by far the largest contribution to cancer. Specifically, in the UK, Denmark and the USA, smoking accounted for

15%, 15% and 19% of all cancers. In the Netherlands, this was 16%. Among Finnish men, smoking caused 23% of all cancer cases, among Finnish women 8%.  $^{14-17}$ 

Variations between countries seem primarily attributable to differences in exposure prevalences. In the Netherlands, relatively large contributions were from physical inactivity (1.9% in the Netherlands vs 0.5% in the UK, and 0.3% in Denmark, although largest (2.9%) in the USA) and PM<sub>9.5</sub> (2.1% in the Netherlands vs 1.1% in Denmark and 1.0% in the UK), whereas relatively small contributions came from cancer-related infections, oral contraceptives and perimenopausal HRT. For overweight and obesity, the estimated contribution was largest in the USA (7.8%) and the UK (6.3%), followed by Finland (4%) for men and 5% for women), the Netherlands (4.2%) and Denmark (3.3%). Ultraviolet exposure is an important risk factor for melanoma of the skin in fair-skinned populations.<sup>20</sup> Largest contributions from ultraviolet exposure were found in Denmark (5.8%) and in the Netherlands (5.3%), while somewhat smaller contributions were found in the USA (4.7%) and in the UK (3.8%).

#### **CONCLUSION**

We estimated that 34% of all newly diagnosed cancer cases in The Netherlands in 2019 were caused by potentially modifiable risk factors. Cigarette smoking, ultraviolet radiation from sunlight, a poor diet and overweight and obesity contributed most significantly. This underscores the potential of effective primary prevention strategies to lower the future burden of cancer, alongside secondary strategies such as screening.

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