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The proportion of postmenopausal breast cancer cases in the Netherlands attributable to lifestyle-related risk factors

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Abstract We aimed to estimate the proportion of Dutch postmenopausal breast cancer cases in 2010 that is attributable to lifestyle-related risk factors. We calculated population attributable fractions (PAFs) of potentially modifiable risk factors for postmenopausal breast cancer in Dutch women aged >50 in 2010. First, age-specific PAFs were calculated for each risk factor, based on their relative risks for postmenopausal breast cancer (from meta-analyses) and age-specific prevalence in the population (from national surveys) around the year 2000, assuming a latency period of 10 years. To obtain the overall PAF, age-specific PAFs were summed in a weighted manner, using the age-specific breast cancer incidence rates (2010) as weights. 95 % confidence intervals for PAF estimates were derived by Monte Carlo simulations. Of Dutch women >40 years, in 2000, 51 % were overweight/obese, 55 % physically inactive (<5 days/week 30 min activity), 75 % regularly consumed alcohol, 42 % ever smoked cigarettes and 79 % had a low-fibre intake (<3.4 g/1000 kJ/day). These factors combined had a PAF of 25.7 % (95 % CI 24.2–27.2), corresponding to 2,665 Dutch postmenopausal breast cancer cases in 2010. PAFs were 8.8 % (95 % CI 6.3–11.3) for overweight/obesity, 6.6 % (95 % CI 5.2–8.0) for alcohol consumption, 5.5 % (95 % CI 4.0–7.0) for physical inactivity, 4.6 % (95 % CI 3.3–6.0) for smoking and 3.2 % (95 % CI 1.6–4.8) for low-fibre intake. Our findings imply that modifiable risk factors are jointly responsible for approximately one out of four Dutch postmenopausal breast cancer cases. This suggests that incidence rates can be lowered substantially by living a more healthy lifestyle.

Keywords Population attributable fraction · Lifestyle-related risk factors · Postmenopausal breast cancer

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Introduction

Breast cancer, especially postmenopausal, is the most occurring cancer in women worldwide and the second leading cause of female cancer death [1]. In Western Europe, one in eight women develops breast cancer during her lifetime, of whom more than 75 % after the age of 50 [2]. The high burden of disease and associated treatment costs makes postmenopausal breast cancer a major public health issue. Not only incidence rates differ according to menopausal status, but effects of some risk factors are also modified by menopausal status. For example, overweight has no or even a small protective effect in premenopausal women, while it increases risk after menopause [3].

Several established risk factors for postmenopausal breast cancer are not, or rather difficult, to modify when the age of 40 has been reached, e.g. age at menarche, parity, age at first child birth and duration of breastfeeding. As lifestyle is modifiable, it provides an opportunity for primary prevention. Overweight and obesity, physical inactivity, alcohol consumption, smoking and low dietary fibre intake are all associated with an increased breast cancer risk after menopause [4–7] and are still present and modifiable at a later age.

The potential impact of preventive measures can be assessed by computing the population attributable fraction (PAF). This fraction represents the proportion of cases in a population that could be prevented if exposure to a causal factor had not occurred [8].

This research is the first to describe the situation for the Netherlands regarding exposure to lifestyle-related risk factors and breast cancer occurrence. We computed individual and combined PAF estimates for the above five lifestyle-related risk factors for the Netherlands, a country with one of the highest incidence rates of breast cancer worldwide [1].

Methods

PAF calculations

The PAF was calculated for four age categories (50–60, 60–70, 70–80, >80 years) for each of the five risk factors individually using the formula [9, 10]: $PAF = 1-1/(P1*RR1 + \ldots + Pn*RRn)$, where P is the prevalence of each exposure, for each exposure level of the risk factor (1 to n), see Table 2 for the different levels of exposure. For example, risk factor BMI has three exposure levels: <25 (reference), 25–30 and >30 kg/m^2. The prevalence is quantified as the percentage of women that is exposed to the risk factor of all middle-aged women. The prevalence is quantified as the percentage of the total population of middle-aged women of women that is exposed to the risk factor. The RR is the relative risk of breast cancer for the risk factor of interest, for each exposure level specific (Table 1). For example, the RR for BMI < 25 kg/m^2 is 1, being the reference, for 25–30 kg/m^2 is 1.15 and for >30 kg/m^2 is 1.33.

We defined postmenopausal breast cancer as all invasive breast malignancies in women aged 50 years or older. A latency period of 10 years between exposure to the hazardous lifestyle and breast cancer occurrence was assumed. Exact information about the true latency period between different exposures and clinical breast cancer presentation is not available. It is however generally accepted that this latency period is about 10 years, which we and others [11] used for our present study.

Therefore, prevalence rates were taken from the years 2000–2001, and 1997 for dietary fibre consumption, of women aged 40 years and older and related to breast cancer occurrence in women of 50 years and older in the year 2010.

To estimate an overall PAF for each risk factor, we first calculated age-specific PAFs for each age category of exposure (40–50, 50–60, 60–70 and 70+). We, therefore, multiplied the risk factors RR by the prevalence of exposure in each age category. Second, we calculated the number of preventable or attributable cases per age category in 2010 (in women aged 50 and over) by multiplying the age-specific PAFs by the number of incident invasive breast cancer cases in 2010 in the corresponding age category. In the third step, the number of attributable cases in each age category was summed over all ages and divided by the total number of invasive breast cancers diagnosed in 2010 in women aged 50 and over. By this method, we incorporated that the prevalence of exposure and the number of invasive breast cancers vary across age categories.

To estimate the PAF of postmenopausal breast cancer for five risk factors combined, summing of the five separate PAFs would lead to an overestimation of the attributable proportion of cases because women may be exposed to more than 1 risk factor. The following multiplicative formula was proposed which, under the assumption of independent exposures and effects, considers the overlap between risk factors within individuals [12]: PAF (joint risk factors) = $1-(1-PAFx\_{1})*(1-PAFx\_{2})*\ldots(1-PAF_{x\_n})$, where x_{1} to x_n refers to the different risk factors being the five lifestyle-related risk factors in our current analysis.

We used a 20,000-fold Monte Carlo simulation to derive 95 % confidence intervals (95 % CI) for the PAF estimates for each risk factor and joint. Monte Carlo simulation uses random sampling according to a specified data distribution taking into account the precision of each RR and

Table 1 Estimated relative risks for five lifestyle-related risk factor and breast cancer

Risk factor	RR (95 % CI)[a]	Mean level within risk category	Comment	Source
BMI (kg/m^2)			Continuous RR of 1.13 (95 % CI 1.08–1.18) per 5 kg/m^2	World Cancer Research Fund [6]
<25	Reference	21.9 kg/m^2		
25–30	1.15 (1.09–1.21)	27.6 kg/m^2		
>30	1.33 (1.19–1.49)	33.8 kg/m^2		
Physical inactivity			Days per week of at least 30 min of moderate intensity physical activity[b]. Continuous RR of 1.05 (95 % CI 1.03–1.07) per 2 h activity/week.	Wu et al. [7]
Active 5 days/week	Reference	170 min/day[c]	The reference category is based on (inter)national guidelines for physical activity [39].	
Active 3–4 days/week	1.06 (1.03–1.08)	152 min/day[c]		
Active 1–2 days/week	1.07 (1.04–1.10)	147 min/day[c]		
Inactive	1.34 (1.19–1.51)	73 min/day[c]		
Alcohol (glass/day)			Continuous RR of 1.08 (95 % CI 1.05–1.10) per glass/day	World Cancer Research Fund [6]
Never drinker	Reference	0 glasses/day		
<1	1.05 (1.03–1.06)	0.5 glasses/day		
1–3	1.20 (1.12–1.28)	1.9 glasses/day		
4+	1.64 (1.35–1.97)	5.2 glasses/day		
Smoking			Categorical RR	Gaudet et al. [5]
Never	Reference			
Past	1.09 (1.04–1.15)			
Current	1.12 (1.08–1.16)			
Dietary fibre (g/1000 kJ/day)			Continuous RR of 0.95 (95 % CI 0.91–0.98) per 10 g/day	Aune et al. [4]
>3.4	Reference	27 g/day	The reference is based on (inter)national recommendations for dietary fibre intake [40, 41]	
2–3.4	1.03 (1.01–1.06)	21 g/day		
<2	1.07 (1.03–1.13)	14 g/day		

For BMI, physical inactivity, alcohol and fibre intake, a continuous RR available from the literature was converted in an RR that matched the mean level of exposure in each risk factor category as observed from the population exposure rates. For example, based on the literature-derived RR for overweight/obesity of 1.13 per five units of increase in BMI, and a mean BMI of 21.9 kg/m^2 in the reference category, 27.6 kg/m^2 in the overweight category, and 33.8 kg/m^2 in the obese category, the risk category associated RRs compared to the reference are $1.13^{(27.6-21.9)/5} = 1.15$, and $1.13^{(33.8-21.9)/5} = 1.33$ (outcome based on the calculation by using exact numbers)

[a] Relative risk (RR) and 95 % confidence interval (95 % CI)

[b] The questionnaire included both occupational and non-occupational activities

[c] Average number of minutes per week were derived from activity diaries which were filled in by a subsample of participants. Reported activity in the diaries includes all types of physical activity, irrespective of intensity level

prevalence estimate. RRs and prevalence rates were independently sampled in each Monte Carlo trial from a log-normal distribution (based on a literature-derived RR estimate with 95 % CI) and a beta distribution, respectively [13]. Analyses were performed using R statistics software, version 3.0.2.

Risk factors and relative risks

We considered lifestyle-related—thus potentially modifiable—risk factors for postmenopausal breast cancer with sufficient scientific proof for a causal association (i.e. judged by the World Cancer Research Fund as 'probable' or 'convincing' causally related [6], or with a large body of evidence based on other scientific literature [4, 5]). Furthermore, we evaluated risk factors that are currently present in middle-aged women in the Netherlands and only those which can be modified at a later age.

We derived RRs adjusted for confounding factors from meta-analyses [4–7] (see Online Resource 1 for more information). For each risk factor, a theoretical optimum level of exposure was defined and used as the reference level, with a corresponding RR of one. Reference exposures were zero where possible (e.g. zero units of alcohol intake per day), or when this was physiologically impossible, the advised level by (inter)national health guidelines was taken (e.g. a BMI < 25 kg/m^2) (see Table 1).

For overweight/obesity (defined by BMI), physical activity, alcohol and fibre intake, a continuous RR was obtained from the literature, assuming a log-linear association between exposure and risk increase [4, 6, 7]. To match these continuous RRs with categorised risk factor prevalence rates, we calculated new categorical RRs based on the literature-derived continuous RR. These categorical RRs were combined with the mean exposure level within each risk factor category, as observed from the population exposure rates (for an example see footnote Table 1).

Prevalence of exposure

Age-specific prevalence rates of risk exposure were derived from large national surveys or registration databases in 1997 [14] and 2000–2001 [15–17]. Detailed information about these surveys is available in the online supplement.

Results

Prevalence rates

Table 2 presents the prevalence rates of exposure to lifestyle-related risk factors in women >40 years of age in the Netherlands in 2000–2001 and 1997. Of these women, on average 51 % were overweight/obese, which increased with age from 40 to 56 % in the ages 40–50 and >70 years, respectively. On average 55 % were estimated to be less active than prescribed by physical activity guidelines (i.e. 5 days/week 30 min of moderate intensity physical activity). Non-adherence to the national activity guideline also modestly increased with age (i.e. 53 % in 40–50 years, and 58 % in >70 years). Alcohol was regularly consumed by on average 75 % of women. Consumption was less prevalent in older than younger women (61 % in >70 years, versus 84 % in 40–50 years). Of all women, an average of 42 % reported to be currently smoking, or smoked in the past, which decreased with an increasing age (54 % in women aged 40–50 and 28 % in women aged >70 years). Dietary fibre intake was below the recommended level in on average 97 % of women, being lowest in women aged 40–50 (85 %).

Population attributable fraction of postmenopausal breast cancer

The estimated PAFs for the separate and combined risk factors are presented in Table 3. PAFs varied across age categories, as a result of the above-described differences in prevalence rates. Overweight/obesity had the highest PAF of 8.8 % (95 % CI 6.3–11.3) (on average for all age categories). The PAF increased with age, from 7.3 % in ages 50–60, to maximum 10 % in women >70 years. Alcohol consumption had the second highest overall PAF of 6.6 % (95 % CI 5.2–8.0). This PAF decreased with age from 7.4 % in 50–60 years to 3.9 % in >80 years. Physical activity had an average PAF of 5.5 % (95 % CI 4.0–7.0), ranging from 4.9 % in ages 50-60, to 7.8 % in women >80. Smoking had an average PAF of 4.6 % (95 % CI 3.3–6.0), which was highest in younger women (i.e. 5.6 % in ages 50–60), and decreased with age (2.9 % in ages >80). Low-fibre intake had a PAF of 3.2 % (95 % CI 1.6–4.8) for all age categories, which was highest in younger women (i.e. 3.7 %, ages 50–60).

Combined, these risk factors accounted for an estimated 25.7 % (95 % CI 24.2–27.2) of all 10,367 postmenopausal breast cancer cases in the Netherlands in 2010 [2]. This implies 2,665 excess cases due to these five risk factors (see Table 3).

Discussion

Our results imply that approximately one out of four postmenopausal breast cancer cases in women aged >50 years in 2010 was attributable to lifestyle factors as present at age 40 and older. Overweight/obesity (8.8 %) contributed the most, followed by alcohol consumption (6.6 %), physical inactivity (5.5 %), smoking (4.6 %) and suboptimal dietary fibre intake (3.2 %). These estimates were based on comprehensive and up-to-date literature and matched with detailed prevalence rates of risk factor exposure in the Netherlands.

Estimations of the attribution of these modifiable lifestyle risk factors to postmenopausal breast cancer have not been described for the Netherlands previously. Furthermore, in this research, we replicated the results of other western European countries of population attributable risks of lifestyle-related risk factors for breast cancer.

Strengths of our study include detailed data on prevalence of risk factor exposure, allowing us to use continuous RRs that ensured little loss of information. In addition, we used RRs which were derived from recent meta-analyses

Table 2 Prevalence rates of risk factor exposure among Dutch women per age category (in 2000–2001)

Risk factor	Prevalence (%)				Source
	40–50 years	50–60 years	60–70 years	>70 years	
BMI (kg/m^2)					Ongoing national survey on living conditions and welfare (Dutch acronym POLS) [15]
<25	60	51	43	44	
25–30	30	35	42	41	
>30	10	14	15	15	
Number of people in the survey[a]	744	612	440	340	
Physical inactivity[b]					National survey on accidents and physical activity (Dutch acronym OBIN) [16]
Active 5 days/week	46	47	44	42	
Active 3–4 days/week	27	28	28	23	
Active 1–2 days/week	21	18	19	17	
Inactive	6	6	9	17	
Number of people in the survey	808	845	688	557	
Alcohol (glass/day)					Ongoing national survey on living conditions and welfare (Dutch acronym POLS) [15]
Never drinker	17	18	28	39	
<1	49	44	50	45	
1–3	32	36	36	16	
4+	3	2	2	0	
Number of people in the survey	569	534	368	265	
Smoking					STIVORO, national survey on adult smoking behaviour [17]
Never	46	51	65	72	
Past	18	19	16	13	
Current	36	30	20	15	
Number of people in the survey	2041	1407	1466	1676	
Dietary fibre (grams/day)[c]					Dutch National Food Consumption Survey (Dutch acronym VCP 1997/1998) [14]
>3.4	15	21	28	23	
2–3.4	54	60	56	64	
<2	31	20	16	14	
Number of people in the survey	579	369	265	249	

The presented numbers are rounded, and may therefore not always add up to 100 %

[a] BMI: number of people in the survey were calculated by the reported standard error of the prevalence rates

[b] Active is defined as at least 30 min of moderate to vigorous physical activity per day, including occupational and non-occupational activities

[c] Prevalence rates of low-fibre intake are based on the years 1997–1998

[4–7] evaluating multiple studies with risk estimates that were adjusted for several confounders, including lifestyle-related risk factors. Furthermore, Monte Carlo simulations were performed to compute 95 % confidence intervals for the PAF estimates, incorporating imprecision in RRs (defines by the literature derived 95 % confidence intervals of the RR estimates) and prevalence rates (including the most detailed prevalence rates available for levels of exposure, for example, for alcohol we used prevalence rates per each glass/day also for the exposure levels >4 glasses/day).

However, there are also some limitations. We cannot rule out possible residual confounding which could have influenced our PAF estimates. However, since the literature-derived RRs incorporated in the meta-analyses usually are adjusted for most important confounders, it is unlikely that remaining unmeasured confounders influenced the results considerably. Simulation studies show that estimates which are corrected for major confounders are affected minimally after additional correction for more possible confounders [18]. Nevertheless, measuring lifestyle habits in a valid way is difficult due to measurement errors in assessing the confounders.

Prevalence rates were based on self-reported exposure. Misclassification (most likely due to underreporting of exposure) may have led to an underestimation of our PAFs. Also, the prevalence rates were measured in a subsample of people, wherein response rates were high (60 %) but not 100 %. Therefore, also participation bias may have affected the results. Furthermore, we included exposure to risk factors from age 40 on only, while it is also likely that not

Table 3 Population attributable fraction (PAF) for five lifestyle-related risk factors and postmenopausal breast cancer

Age at exposure	Age at outcome	Observed cases in 2010[a]	Risk factor									
			Overweight/obesity (BMI > 25 kg/m^2)		Physical inactivity		Alcohol consumption		Smoking		Low-fibre intake	
			PAF (95 % CI)	Excess cases	PAF (95 % CI)	Excess cases	PAF (95 % CI)	Excess cases	PAF (95 % CI)	Excess cases	PAF (95 % CI)	Excess cases
40–50	50–60	3362	7.3 %	246	4.9 %	164	7.4 %	250	5.6 %	189	3.7 %	124
50–60	60–70	3367	9.1 %	305	4.8 %	161	7.6 %	256	5.0 %	169	3.1 %	105
60–70	70–80	2016	10.0 %	202	5.7 %	115	5.8 %	116	3.6 %	74	2.8 %	56
>70	>80	1622	9.9 %	161	7.8 %	126	3.9 %	64	2.9 %	47	2.9 %	47
	Total	10,367	8.8 % (6.3–11.3)	913	5.5 % (4.0–7.0)	566	6.6 % (5.2–8.0)	686	4.6 % (3.3–6.0)	479	3.2 % (1.6–4.8)	332
			PAF for all five risk factors combined: 25.7 % (95 % CI 24.2–27.2)									

[a] Data from the Dutch national cancer registry [2]

The 95 % confidence intervals (95 % CI) were derived from Monte Carlo simulations. The presented numbers are rounded, the calculations were performed with the use of exact numbers

only short-term, but also life-long exposure to lifestyle-related risk factors, or exposure during a critical period of life (e.g. between menarche and first childbirth) contributes to a higher breast cancer risk [19]. However, there is still much uncertainty around the latency period and which period in life is most influential.

In comparable research, hormone replacement therapy (HRT) is often included as a risk factor. Although RRs of 1.10 to 1.66 have been described for current HRT use [20, 21], we did not include this factor in our analysis. In 2001, the estimated prescription of HRT in women > 40 in the Netherlands was 5.6 % and dropped to 2.4 % in 2004 [22]. Currently, prescriptions are close to zero [23]. As shown by the Million Women study, the increased risk of breast cancer caused by HRT almost disappears after 5 years of cessation [21], meaning that HRT use (past and current) barely influences breast cancer incidence in the Netherlands anymore.

Attributable fractions of modifiable risk factors for all age breast cancer have been estimated for several countries in Europe, reaching up to 25 % in the UK and Germany [24, 25]. However, different sets of risk factors were considered, making results difficult to compare.

Regarding the whole of Europe, Soerjomataram et al. [26], estimated the number of excess cases, i.e. avoidable breast cancer cases, by comparing a countries all-ages incidence rate to the lowest incidence rate in a European country (the baseline incidence rate). For the Netherlands, they estimated around 30 % of all age breast cancer to be avoidable, which was comparable to their estimates for other Western and Northern European countries, but much higher than estimates for Eastern (i.e. Czech Republic, Romania, Lithuania; up to approximately 5 %) and Southern Europe (i.e. Spain, Portugal; up to approximately 15 %). The authors speculate that this higher incidence rate could be caused by over-diagnosis due to extensive screening programmes and higher exposure to reproduction-linked risk factors. Even though these estimates cannot be directly compared to our PAF numbers, as they used a different methodology, it gives us an idea about the Dutch situation in proportion to the rest of Europe with regard to avoidable cancer cases. And although their number refers to all age breast cancer, it will largely refer to postmenopausal breast cancer as most cases occur after age 50.

We included five lifestyle-related risk factors for postmenopausal breast cancer for which a large body of evidence is available and that occur with substantial prevalence rates in middle-aged women in the Netherlands.

Fibre intake and smoking are not, or seldom, considered when estimating PAFs for breast cancer. Since there is emerging strong evidence that these factors increase breast cancer risk, we included these factors and recommend including them in future studies. A recent Canadian study that included smoking as a risk factor reported a PAF of 3–4 % based on prevalence rates of risk facture exposure in the years 1994–2006 [27].

Overweight and obesity, alcohol consumption and physical inactivity are often included in other studies. Considering these three factors, we estimate a combined PAF of around 20 %. Similar results were found for neighbouring countries. Parkin et al. estimated that 17 % of all breast cancer cases, irrespective of age, in 2011 were attributable to these factors in the UK [24]. Barnes et al. estimated a PAF of 21 % for Germany in 2010 [25]. However, we observed some differences for the separate risk factors. PAF estimates for a BMI > 25 kg/m^2 vary from 2.5 % in Germany [25], to 5.6 % in France [28] and 8.7 % in the UK [29], the latter being comparable to our estimate (8.8 %). The attribution of overweight/obesity has previously been computed for the Netherlands. Bergstrom et al. estimated a PAF of 6.3 % based on a 42 % exposure rate in the years 1993–1996, and similar RRs as we used [30]. Since the prevalence of overweight/obesity is still increasing in the Western world, the PAF is doing so concordantly.

For alcohol consumption, similar PAFs, ranging from 6.4 to 9.4 %, are described in adjacent countries [25, 28, 31]. However, PAFs for alcohol consumption differ in other developed countries as the US and Australia, where PAFs reach up to maximum 3 % [27, 32, 33]. Consumption of alcohol by European women is rather high; 75 % of Dutch women >40 years drink on a regular basis.

For physical inactivity, mainly higher PAF estimates than ours (5.5 %) were reported in Europe, of around 10–14 % [25, 28, 34], except for the UK (3.4 %) [35]. Numbers in the U.S. even rise up to 16 % [36]. Differences in prevalence rates largely explain this variation, i.e. in the U.S., 78 % of women were considered physically inactive, versus 56 % in the Netherlands. Another explanation why estimates vary greatly could lie in the fact that PAFs are sensitive to differences in risk category definitions with their accompanying RR [37]. Due to the great difficulty of measuring activity levels and determining proper risk categories, other definitions for physical inactivity and RRs are used in literature. Also, we did not incorporate intensity of activities.

In the Netherlands, incidence of breast cancer is among the highest worldwide. We estimated that approximately 25 % of postmenopausal breast cancer is associated with lifestyle behaviour at age 40 years. Reproductive factors and hormones will be associated with another proportion of cases, but these are less modifiable. Still, there is a substantial proportion of cancers that seem to occur at random [38]. However, we should also not exclude the possibility of yet undetected exposures, such as naturally occurring estrogens in the environment; or other chemicals with estrogenic function.

Often, success rates of lifestyle modifying programmes are limited. Therefore, for the Netherlands, a 25.7 % reduction in postmenopausal breast cancer incidence would be the maximum to be achieved, rather than realistic. However, these estimates may help motivating women as well may they inform policy makers about which risk factors should be addressed first.

To conclude, our results imply that one in four postmenopausal breast cancer cases in the Netherlands in 2010 is attributable to five strongly associated lifestyle-related risk factors. These risk factors are excess body weight, an inactive lifestyle, alcohol consumption, smoking and low dietary fibre intake.

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