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Proportion of premenopausal and postmenopausal breast cancers attributable to known risk factors: Estimates from the E3N-EPIC cohort

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Breast cancer is the most frequently diagnosed cancer among women worldwide. Breast cancer risk factors have been widely explored individually; however, little is known about their combined impact. We included 67,634 women from the French E3N prospective cohort, aged 42–72 at baseline. During a 15-year follow-up period, 497 premenopausal and 3,138 postmenopausal invasive breast cancer cases were diagnosed. Population-attributable fractions (PAFs) were used to estimate cases proportions attributable to risk factors under hypothetical scenarios of lowest exposure. We examined overall premenopausal and postmenopausal invasive breast cancers and tumour subtypes (ER status and HER2 expression). Premenopausal breast cancer was not significantly attributable to non-behavioral (61.2%, −15.5 to 91.88%) nor to behavioral (39.9%, −71.0 to 93.9%) factors, contrary to postmenopausal breast cancer (41.9%, 4.5 to 68.7% and 53.5%, 12.8 to 78.7%, respectively). Individually, the highest statistically significant PAFs were obtained in premenopause for birth weight (33.6%, 5.7 to 56.6%) and age at menarche (19.8%, 5.2 to 33.6%) for non-behavioral factors and in postmenopause for history of benign breast diseases (14.9%, 11.6 to 18.0%) and age at menarche (9.7%, 3.9 to 15.5%) for non-behavioral factors and for body shape at menarche (17.1%, 9.7 to 24.3%), use of hormone replacement therapy (14.5%, 9.2 to 19.6%), dietary pattern (10.1%, 2.6 to 17.4%) and alcohol consumption (5.6%, 1.9 to 9.3%) for behavioral factors. These proportions were higher for ER+, HER2− and ER+/HER2− postmenopausal breast cancers. Our data support the hypothesis that in postmenopause, never starting unhealthy behaviors can reduce the number of diagnosed breast cancers.

Key words: breast cancer, women, risk factors, cohort study, estrogen receptor, hormone receptor, postmenopausal women, premenopausal women, attributable fraction, hormone replacement therapy, birth weight

Abbreviations: BBD: benign breast disease; BMI: body mass index; CI: confidence intervals; E3N: *Étude Épidémiologique des femmes de la Mutuelle Générale de l'Éducation Nationale*; FFTP: first full-term pregnancy; HR: hazard ratio; ICD-10: International Classification of Diseases, 10th edition; MET: metabolic equivalent task; MGEN: *Mutuelle Générale de l'Éducation Nationale*; ; MHT: menopause hormone therapy; PAF: population-attributable fraction; UVRd: ultraviolet radiation doses

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What's new?

Many risk factors for breast cancer have been identified, both behavioural and non-behavioural. However, little is known about what proportion of cases are due to each type of factor. In this study, the authors found that a higher proportion of premenopausal breast cancers was associated with non-behavioural factors, while for postmenopausal cases, behavioural factors such as alcohol consumption, diet, weight, and hormone therapy had the greatest impact. These data support the hypothesis that, for postmenopausal breast cancer, avoiding unhealthy behaviours may reduce the number of diagnosed cases.

Breast cancer is the most frequently diagnosed neoplasm among women, with an incidence reaching 43.3 per 100,000 woman-years worldwide in 2012.[1] Risk factors for breast cancer have been widely explored and include reproductive and genetic factors, anthropometry, and lifestyle factors. They are either of a behavioral (such as daily alcohol consumption) or a non-behavioral (such as a family history of breast cancer) nature.[2]

Taking into account the prevalence of the risk factors and their association with the disease allows the computation of the population-attributable fraction (PAF) that quantifies the burden of a disease and helps focus prevention strategies.[3] PAFs enable an estimation of the proportion of cases attributable to one or several exposures: the artificial removal of these exposures could potentially prevent those cases. Previously published combined PAFs for breast cancer risk factors have been estimated from several observational studies of women in the US,[4–7] Germany,[8] Iran,[9] Italy,[10,11] Sweden[12] and Great Britain.[13] However, only a few of these studies assessed the combined effect of several risk factors simultaneously,[6,7,13] few were prospective studies exempt of recall bias,[4,12] or accounted for menopausal status.[6–11]

Although recent studies have provided evidence of the differential association between risk factors and breast cancer incidence according to the expression of the Human Epidermal Growth Factor Receptor 2 (HER2) protein and the oestrogen-receptor (ER) status of the tumour,[14,15] differences in PAFs accounting for ER subtypes have been evaluated in only one study,[8] and no study evaluated PAFs according to HER2 subtypes.

Based on data from the large prospective E3N-EPIC cohort study, we estimated the PAFs of several subtypes of invasive breast cancers (premenopausal, postmenopausal, ER and HER2 subtypes) corresponding to individual and combined behavioral and non-behavioral breast cancer risk factors.

Material and Methods

Study population

The E3N (*Étude Épidémiologique auprès des femmes de la Mutuelle Générale de l'Éducation Nationale (MGEN)*) prospective cohort was launched in 1990 to investigate risk factors for cancer in women.[16] The cohort included 98,995 French women who were regularly asked about their health status and lifestyle. Self-administered questionnaires were sent every 2 to 3 years to update the information. All women signed an informed consent form, in compliance with the rules of the French National Commission for Data Protection and Privacy from which approval was obtained.

For the present study, follow-up started at the return date of the 1993 questionnaire, which first recorded dietary habits, thereafter considered as baseline. Responders ($N = 74{,}522$) contributed person-years of follow-up until the date of any cancer diagnosis other than basal cell skin carcinoma, the date of the last completed questionnaire or the date the last available questionnaire was mailed (June 2008), whichever occurred first. We excluded women diagnosed with a cancer before baseline ($N = 4{,}705$), those with no follow-up questionnaire ($N = 769$), and cancer cases with no specified date of diagnosis ($N = 54$). In addition, we excluded women with unlikely values for the ratio between energy intake and required energy (*i.e.*, the lowest and highest percentile for the cohort, $N = 1{,}360$). Our final population for analysis consisted of 67,634 women, aged 42–72 years at baseline.

Data collection

Women were considered postmenopausal if they reported amenorrhea for more than one year (unless due to hysterectomy) or if they self-reported that they were postmenopausal.[17] Women with a hysterectomy were then considered postmenopausal only if they self-reported that they were postmenopausal.

Categorizations and references used for each risk factor are specified in Tables 1 and 2 and were based on the literature.[2] Non-behavioral variables included risk factors on which we cannot directly act, while behavioral variables included all other risk factors.

Non-behavioral risk factors

Benign breast disease (BBD) included self-reported adenomas and fibrocystic diseases. Self-reported age at menarche was recorded in 1992, with an age ranking from 8 to 19 years. Low birth weight was defined as below 2.5 kg, normal birth weight as between 2.5 and 4.0 kg, and high birth weight as over 4.0 kg. Because preterm and low weight full-term babies have been associated with different levels of breast cancer risk,[18] premature babies were considered as missing values for birth weight. Age at menopause was defined as age at last menstrual period, age at bilateral oophorectomy, or self-reported age at menopause.[17] First-degree family history of

Table 1. Non-behavioral baseline characteristics and multivariate-adjusted hazard ratios with 95% confidence intervals regarding invasive breast cancer among premenopausal and postmenopausal women, E3N cohort ($N = 67,634$)

		Invasive premenopausal breast cancer cases		Invasive postmenopausal breast cancer cases	
	Non cases $N = 63,999$	$N = 497$	HR (95%CI)	$N = 3,138$	HR (95%CI)
Age (years)[1]					
Mean (SD)	52.75 (6.66)	46.77 (2.51)	–	55.28 (5.04)	–
Age at cancer diagnosis (years)					
Mean (SD)	–	50.55 (2.90)	–	62.08 (6.50)	–
Menopausal status					
Premenopausal	28,675 (44.81)	497 (100.00)	–	1,063 (33.88)	–
Postmenopausal	35,324 (55.19)	–	–	2,075 (66.12)	–
First-degree family history of breast cancer[2]					
At least one	4,587 (7.17)	46 (9.25)	**1.37 (1.01 to 1.86)**	345 (10.99)	**1.50 (1.34 to 1.69)**
None	49,746 (77.73)	386 (77.67)	Reference	2,321 (73.97)	Reference
Missing	9,666 (15.10)	65 (13.08)	1.11 (0.85 to 1.45)	472 (15.04)	0.99 (0.90 to 1.10)
Level of education					
Undergraduate	7,192 (11.24)	33 (6.64)	Reference	340 (10.83)	Reference
Graduate	34,019 (53.15)	251 (50.50)	1.15 (0.80 to 1.66)	1,642 (52.33)	1.00 (0.89 to 1.13)
Post-graduate	22,788 (35.61)	213 (42.86)	1.05 (0.72 to 1.53)	1,156 (36.84)	1.07 (0.94 to 1.21)
Height at adulthood (cm)					
<160	21,922 (34.25)	138 (27.77)	Reference	1,036 (33.02)	Reference
[160; 165)	22,394 (34.99)	177 (35.61)	1.06 (0.85 to 1.33)	1,089 (34.70)	1.04 (0.95 to 1.13)
[165; 170)	13,955 (21.81)	119 (23.94)	1.04 (0.81 to 1.33)	702 (22.37)	1.09 (0.99 to 1.21)
≥ 170	5,728 (8.95)	63 (12.68)	1.18 (0.87 to 1.61)	311 (9.91)	**1.20 (1.05 to 1.37)**
History of benign breast disease[3]					
At least one, with at least one biopsy performed	1,556 (2.43)	20 (4.02)	**2.02 (1.37 to 2.99)**	131 (4.17)	**1.75 (1.52 to 2.02)**
At least one, no biopsy performed	16,860 (26.34)	177 (35.61)	**1.42 (1.18 to 1.71)**	1,054 (33.59)	**1.48 (1.37 to 1.60)**
None	45,583 (71.23)	300 (60.37)	Reference	1,953 (62.24)	Reference
Age at menarche (years)					
<10	205 (0.32)	2 (0.40)	1.43 (0.35 to 5.81)	13 (0.42)	1.58 (0.91 to 2.74)
[10; 12)	12,758 (19.93)	98 (19.72)	1.26 (0.95 to 1.66)	649 (20.68)	**1.19 (1.07 to 1.32)**
[12; 14)	33,177 (51.84)	291 (58.55)	**1.36 (1.09 to 1.70)**	1,651 (52.61)	**1.13 (1.04 to 1.23)**
≥ 14	17,859 (27.91)	106 (21.33)	Reference	825 (26.29)	Reference
Birth weight					
Low (< 2.5kg)	3,466 (5.41)	14 (2.82)	Reference	154 (4.91)	Reference
Normal (2.5–4 kg)	46,189 (72.17)	360 (72.43)	**1.72 (1.01 to 2.95)**	2,321 (73.96)	1.13 (0.96 to 1.33)
High (≥4 kg)	3,531 (5.52)	31 (6.24)	**1.99 (1.05 to 3.76)**	163 (5.19)	1.03 (0.82 to 1.29)
Missing	10,813 (16.90)	92 (18.51)	**2.32 (1.32 to 4.08)**	500 (15.94)	**1.34 (1.11 to 1.60)**
Age at menopause (years, for postmenopausal women)[4]					
< 48	10,426 (16.29)		–	489 (15.58)	Reference
[48; 50)	10,275 (16.06)		–	548 (17.46)	1.09 (0.97 to 1.23)

Table 1. Non-behavioral baseline characteristics and multivariate-adjusted hazard ratios with 95% confidence intervals regarding invasive breast cancer among premenopausal and postmenopausal women, E3N cohort ($N = 67,634$) (Continued)

		Invasive premenopausal breast cancer cases		Invasive postmenopausal breast cancer cases	
	Non cases $N = 63,999$	$N = 497$	HR (95%CI)	$N = 3,138$	HR (95%CI)
[50; 52)	18,587 (29.04)		–	993 (31.65)	**1.11 (1.00 to 1.24)**
[52; 54)	13,251 (20.71)		–	623 (19.85)	1.03 (0.92 to 1.16)
≥ 54	9,673 (15.11)		–	485 (15.46)	**1.17 (1.03 to 1.34)**

NOTE: Bold values means p values<0.05.
HRs were adjusted on age (as the time scale), first-degree family history of breast cancer, level of education, height at adulthood, history of benign breast diseases, age at menarche, birth weight, age at menopause (for postmenopausal women only), tobacco smoking, number of children and age at FFTP, physical activity level, body shape at menarche, breastfeeding, dietary pattern, alcohol consumption, vitamin D intake and UVRd, oral contraceptives or progesterone alone use, body mass index and menopausal hormone therapy use (for postmenopausal women only).
[1]Age was considered as the timescale in Cox regression models, which did not allow the estimation of HR associated with age.
[2]Family history of breast cancer included history among first-degree relatives (mother, sisters and daughters).
[3]Benign breast diseases included adenomas and fibrocystic diseases.
[4]Non cases included 28,675 (44.81%) of women who were premenopausal at baseline.

breast cancer, level of education and height at adulthood were assessed at baseline. Level of education has been considered as a non-behavioral risk factor as an approximation of the socioeconomic status.

Behavioral risk factors

Overall physical activity included walking, gardening, home improvement, floor climbing, cycling and other sports; durations were averaged over the summer and winter. The assigned metabolic equivalent task (MET) values per hour were 3.0 for walking, 4.0 for gardening, 4.5 for home improvement, 0.067 for each floor climbed and 6.0 for cycling and other sports.[19] The total number of months women had spent breastfeeding was calculated by summing the months of breastfeeding for each birth. Nulliparous women were considered as never having breastfed. Body shape around menarche was assessed using drawings in a series of Sørensen's body shapes,[20] referring to body shapes ranging from 1 (thin) to 8 (obese). Body shapes 4 to 8 were combined because of small numbers of women in these categories.

At baseline, women were asked to fill in a dietary questionnaire, using quantitative and qualitative estimates of consumed items.[21] Dietary patterns were computed from a factor analysis, based on 57 predefined food groups, using a principal component analysis. We extracted the first two factors, respectively labeled "Healthy pattern" and "Western pattern" (see Ref. 22 for further explanations), and created a four-modality variable, using the median value of both of the dietary scores as thresholds. Alcohol consumption and dietary vitamin D were extracted from the dietary questionnaire using a food composition table derived from the updated French national database.[23] Baseline regions of residence were linked to a database containing mean daily ultraviolet radiation doses (UVRd in kJ/m^2/day) in French departments.[24] Daily dietary vitamin D and UVRd were compiled into a four-modality variable, using the median value of both variables as thresholds.[25]

BMI was computed as weight/height^2 in kg/m^2. Lifetime menopause hormone therapy (MHT) use included any systemic use of oestrogens (alone or combined with a progestagen) or tibolone. Vaginally administered oestrogens and estriol were not considered as hormone therapy because they have not been found associated with breast cancer risk.[26,27] At each questionnaire, a woman was considered as a recent user of a specific type of MHT when she reported any use within the preceding 12 months.

Tobacco smoking, number of deliveries (born alive child or stillbirth) and age at first full-term pregnancy were assessed at baseline. Use of oral contraceptive and progestagen alone were assessed throughout the follow-up.

Ascertainment of cancer cases

All questionnaires enquired about any cancer occurrence, type of cancer, addresses of physicians and permission to contact them. Only invasive breast cancers were considered, and *in situ* tumors with no concomitant invasive tumor were censored at the date of diagnosis. Invasive breast cancer cases were confirmed by pathology reports, obtained for 91.5% of cases. Information on oestrogen-receptor (ER) status and on the expression of the human epidermal growth factor receptor 2 (HER2) were extracted from pathology reports. Invasive premenopausal breast cancers were classified accordingly into two categories, ER+ and ER−, and invasive postmenopausal breast cancer into eight non-exclusive categories: HER2+, HER2−, ER+, ER− and their combinations.

Statistical methods

Multivariate Cox proportional hazards regression models with age as the timescale[28] were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of breast cancer risk associated with the risk factors mentioned above. Models were stratified by menopausal status because of the

Table 2. Behavioral baseline characteristics and multivariate-adjusted hazard ratios with 95% confidence intervals regarding invasive breast cancer among premenopausal and postmenopausal women, E3N cohort ($N = 67,634$)

		Invasive premenopausal breast cancer cases		Invasive postmenopausal breast cancer cases	
	Non cases $N = 63,999$	$N = 497$	HR (95%CI)	$N = 3,138$	HR (95%CI)
Tobacco smoking					
Current smoker	8,747 (13.67)	74 (14.89)	0.96 (0.71 to 1.28)	395 (12.59)	0.99 (0.88 to 1.13)
Past smoker	34,257 (53.53)	229 (46.08)	1.15 (0.95 to 1.40)	1,684 (53.66)	1.01 (0.94 to 1.09)
Never smoker	20,995 (32.80)	194 (39.03)	Reference	1,059 (33.75)	Reference
Number of children and age at FFTP					
One child before 30	7,115 (11.12)	51 (10.26)	0.99 (0.73 to 1.34)	325 (10.36)	0.99 (0.88 to 1.12)
One child after 30	2,828 (4.42)	38 (7.65)	**1.64 (1.16 to 2.31)**	164 (5.22)	**1.29 (1.09 to 1.51)**
More than one child, the first before 30	42,829 (66.92)	314 (63.18)	Reference	1,998 (63.67)	Reference
More than one child, the first after 30	3,847 (6.01)	44 (8.85)	**1.44 (1.04 to 1.98)**	213 (6.79)	**1.22 (1.06 to 1.40)**
Nulliparous	7,380 (11.53)	50 (10.06)	0.97 (0.69 to 1.35)	438 (13.96)	**1.28 (1.13 to 1.45)**
Physical activity level (METs/hour/week)					
< 20	12,951 (20.24)	120 (24.15)	1.06 (0.82 to 1.38)	618 (19.69)	1.02 (0.92 to 1.13)
[20; 40)	21,072 (32.92)	176 (35.41)	1.00 (0.79 to 1.28)	1,033 (32.92)	1.03 (0.94 to 1.13)
[40; 60)	13,652 (21.33)	94 (18.91)	0.91 (0.69 to 1.20)	688 (21.93)	1.03 (0.93 to 1.14)
≥ 60	16,324 (25.51)	107 (21.53)	Reference	799 (25.46)	Reference
Body shape at menarche[1]					
Body shape 1	13,465 (21.04)	86 (17.30)	1.08 (0.80 to 1.45)	751 (23.93)	**1.33 (1.19 to 1.49)**
Body shape 2	22,093 (34.52)	185 (37.22)	**1.28 (1.00 to 1.65)**	1,140 (36.33)	**1.27 (1.15 to 1.41)**
Body shape 3	14,922 (23.32)	130 (26.16)	1.22 (0.93 to 1.59)	704 (22.44)	**1.18 (1.06 to 1.32)**
Body shape ≥ 4	13,519 (21.12)	96 (19.32)	Reference	543 (17.30)	Reference
Breastfeeding (months)					
None	24,032 (37.55)	187 (37.63)	1.09 (0.82 to 1.45)	1,231 (39.23)	1.02 (0.91 to 1.14)
(0; 3)	17,901 (27.97)	134 (26.96)	0.94 (0.71 to 1.25)	858 (27.34)	1.07 (0.95 to 1.19)
[3; 6)	10,279 (16.06)	95 (19.11)	1.03 (0.76 to 1.38)	513 (16.35)	1.11 (0.99 to 1.26)
≥ 6	11,787 (18.42)	81 (16.30)	Reference	536 (17.08)	Reference
Dietary pattern[2]					
Low Healthy score and high Western score	16,158 (25.25)	154 (30.99)	1.05 (0.81 to 1.37)	813 (25.91)	**1.20 (1.08 to 1.33)**
High Healthy and Western scores	15,718 (24.56)	153 (30.78)	**1.36 (1.04 to 1.79)**	821 (26.16)	**1.15 (1.04 to 1.28)**
Low Healthy and Western scores	15,831 (24.73)	100 (20.12)	1.05 (0.78 to 1.40)	761 (24.25)	1.10 (0.99 to 1.22)
High Healthy score and low Western score	16,292 (25.46)	90 (18.11)	Reference	743 (23.68)	Reference
Alcohol consumption (g/day)					
[0; 10)	38,441 (60.06)	302 (60.76)	Reference	1,750 (55.77)	Reference
[10; 20)	13,060 (20.41)	106 (21.33)	1.01 (0.81 to 1.27)	659 (21.00)	1.05 (0.96 to 1.15)
≥ 20	12,498 (19.53)	89 (17.91)	0.89 (0.69 to 1.14)	729 (23.23)	**1.18 (1.07 to 1.29)**
Vitamin D intake (μg) and UVRd ($kJ/m^2/day$)[3]					
Vitamin D intake ≥ 2.38 and UVRd ≥ 2.5	15,329 (23.95)	123 (24.75)	Reference	720 (22.94)	Reference
	16,631 (25.99)	133 (26.76)	0.93 (0.73 to 1.20)	881 (28.08)	**1.14 (1.03 to 1.26)**

Table 2. Behavioral baseline characteristics and multivariate-adjusted hazard ratios with 95% confidence intervals regarding invasive breast cancer among premenopausal and postmenopausal women, E3N cohort ($N = 67,634$) (Continued)

		Invasive premenopausal breast cancer cases		Invasive postmenopausal breast cancer cases	
	Non cases $N = 63,999$	$N = 497$	HR (95%CI)	$N = 3,138$	HR (95%CI)
Vitamin D intake $\geq$ 2.38 and UVRd $<$ 2.5					
Vitamin D intake $<$ 2.38 and UVRd $\geq$ 2.5	17,457 (27.28)	119 (23.94)	0.97 (0.74 to 1.27)	834 (26.58)	1.05 (0.94 to 1.16)
Vitamin D intake $<$ 2.38 and UVRd $<$ 2.5	14,582 (22.78)	122 (24.55)	1.11 (0.85 to 1.46)	703 (22.40)	1.06 (0.95 to 1.18)
Oral contraceptive or progestagen alone use					
Recent[4]	10,763 (16.82)	136 (27.36)	1.07 (0.87 to 1.33)	549 (17.50)	**1.38 (1.18 to 1.61)**
Past, last use $<$ 10 years ago	16,147 (25.23)	138 (27.77)	1.09 (0.87 to 1.37)	870 (27.72)	1.06 (0.97 to 1.15)
Past, last use $\geq$ 10 years ago	14,489 (22.64)	145 (29.17)	Reference	598 (19.06)	Reference
Never	17,132 (26.77)	57 (11.47)		858 (27.34)	
Unknown recency	5,468 (8.54)	21 (4.23)	0.78 (0.46 to 1.29)	263 (8.38)	0.95 (0.82 to 1.09)
Body mass index (kg/m^2)					
$<$ 18.5	2,234 (3.49)	18 (3.62)	1.03 (0.59 to 1.80)	84 (2.68)	Reference
[18.5; 25)	48,383 (75.60)	404 (81.29)	1.15 (0.91 to 1.45)	2,310 (73.61)	
[25; 30)	10,994 (17.18)	62 (12.47)	Reference	610 (19.44)	**1.19 (1.10 to 1.30)**
$\geq$ 30	2,388 (3.73)	13 (2.62)		134 (4.27)	**1.25 (1.07 to 1.46)**
Recent[4] MHT use (for postmenopausal women)[5]					
Oral oestrogens only	1,747 (4.95)		–	108 (3.44)	1.07 (0.92 to 1.23)
Oral oestrogens with progesterone/dydrogesterone	4,621 (13.08)		–	296 (9.43)	**1.20 (1.09 to 1.32)**
Oral oestrogens with other progestagen[6]	5,253 (14.87)		–	412 (13.13)	**1.72 (1.57 to 1.88)**
Other[7]	900 (2.55)		–	57 (1.82)	1.17 (0.96 to 1.44)
No recent MHT	23,728 (67.17)		–	2,322 (74.00)	Reference

NOTE: Bold values means p values < 0.05.
HRs were adjusted on age (as the time scale), first-degree family history of breast cancer, level of education, height at adulthood, history of benign breast diseases, age at menarche, birth weight, age at menopause (for postmenopausal women only), tobacco smoking, number of children and age at FFTP, physical activity level, body shape at menarche, breastfeeding, dietary pattern, alcohol consumption, vitamin D intake and UVRd, oral contraceptives or progesterone alone use, body mass index and menopausal hormone therapy use (for postmenopausal women only).
[1]Body shapes were based on drawings in a series of Sorensen's body shapes.
[2]Dietary patterns were computed from a factor analysis, based on 57 predefined food groups, using a principal component analysis. The first two factors were extracted and respectively labelled "Healthy pattern" and "Western pattern". A four-modality variable was created using the median value of both of the dietary scores as thresholds. Weak adherence means a score under the median value, great adherence a score over the median value.
[3]The average daily vitamin D was estimated from a food composition table. Baseline regions of residence were linked to a database containing mean daily ultraviolet radiation doses (UVRd in kJ/m^2/day). Daily dietary vitamin D and ultraviolet radiation doses were compiled into one four-modality variable, using the median value of daily vitamin D and ultraviolet radiation doses as threshold.
[4]Recent use of oral contraceptive, progestagens alone or MHT was defined as current use or past use within the 12 preceding months.
[5]Non cases included 28,675 (44.81%) of women who were premenopausal at baseline.
[6]Other progestagen included chlormadinone acetate, cyproterone acetate, demegestone, dienogest, drospirenone, ethynodiol acetate, gestodene, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, megestrol acetate, nomegestrol acetate, norethisterone acetate and promegestone.
[7]Other MHT included tibolone and MHT containing an androgen, intramuscularly administered or with no specified formulation.

V-shape relationship between adiposity and breast cancer risk, with a decreased risk before the menopause and an increased risk after.[29,30] Menopausal status, use of MHT, BMI, tobacco smoking, personal history of BBD, and use of oral contraceptives and progestagens alone were updated at each questionnaire and were thus considered as time dependent, whereas all other variables were assessed at baseline, or in 2002 for birth weight. All analyses were adjusted according

to previous mammogram (in the previous follow-up period yes/no, time-dependent variable), and further stratified by cohort of birth ([1925–1930], [1931–1935], [1936–1940], [1941–1945], [1946–1950]).[31].

As the family history of breast cancer and the birth weight variables presented >5% of missing values, missing categories were created for both variables. Causes of missing values for birth weight were prematurity (18.6%), no response to the questionnaire answering about the birth weight (23.5%) and no response to the question (57.9%). For the other variables, missing values were imputed to the modal category for categorical variables and to the median value for quantitative variables.

Estimation of the population-attributable fractions (PAF)

To quantify the attributable proportion of cancer cases, we estimated the population-attributable fraction (PAF) associated with specific behaviors with the assumption of a causal relationship on a particular set of risk factors, all others remaining unchanged. Point estimates and 95% CIs were evaluated using a method for the estimation of PAFs in cohort studies, described by Spiegelman *et al.*[32] The estimation of PAFs took into account exposure prevalence throughout follow-up, based on person-years in the E3N cohort, and HRs of cancer risk associated with exposure and potential effect modifiers.

PAFs were estimated separately for each factor included in the model and expressed as the percentage of cancer cases attributed to a hypothetical scenario in which all women would be in the reference category (described in Tables 1 and 2). In addition, we estimated the combined PAFs of the non-behavioral factors, the behavioral factors and all of them simultaneously, including all factors considered in the individual PAFs, whatever their significance.

We performed stratified analyses according to receptor status. Women with unknown receptor status were excluded from the stratified analyses, and cases with other types of cancer than the one of interest were censored at the date of diagnosis. A positive PAF quantifies the percentage of potentially avoidable cancer cases, a negative PAF the percentage of potentially additional cancer cases. Factors categories took into account in PAFs estimation are described in Tables 1 and 2. Because PAFs were sensitive to threshold choices,[33] variables categorizations were chosen so that 20% or more of the population were in the reference category, whenever possible.

Sensitivity analyses

A complete case analysis was performed by excluding individuals with missing values for at least one specific risk factor. The reverse-causation hypothesis was tested by censoring cancer cases occurring within the first three years of follow-up. Because of correlations between BMI and adult height, and between dietary patterns, alcohol consumption and tobacco smoking, analyses for one variable not adjusting for the other(s) were performed. The association between birth weight and breast cancer risk was tested by performing additional analyses with further adjustment for length at birth and with premature babies considered as a separate category instead of missing values. Finally, a sensitivity analysis excluding non-validated cancer cases was performed to avoid the misclassification of cases.

All analyses were conducted using SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Population characteristics

The 67,634 women included in our analyses were aged 42 to 72 at study entry, with a mean age of 52.8 years (SD = 6.6 years). During 876,468 person-years (median follow-up of 7 years for cases and 13 years for non-cases), 3,635 women were diagnosed with invasive breast cancer; 497 were premenopausal and 3,138 postmenopausal at diagnosis. Baseline characteristics of the population and multivariate HRs from Cox regression models associated with the risk factors used in the estimation of the PAFs are presented in Tables 1 and 2.

Population-attributable fractions of only one risk factor

As univariate and multivariate estimations of PAFs produced similar results, we only present results from multivariate analyses. Table 3 presents PAFs as percentages for one risk factor or a combination of risk factors for premenopausal and postmenopausal invasive breast cancers.

Premenopausal breast cancer. PAFs reaching statistical significance were 14.1% (5.9 to 22.2%) for personal history of BBD, 19.8% (5.2 to 33.6%) for age at menarche (before 14) and 33.6% (5.7 to 56.6%) for birth weight (normal or high), meaning that approximately one out of 7, 5 and 3 premenopausal breast cancers, respectively, could be attributed to these factors.

Postmenopausal breast cancers. PAFs reaching statistical significance were 3.6% (2.5 to 4.8%) for family history of breast cancer, 9.7% (3.9 to 15.5%) for age at menarche and 14.9% (11.6 to 18.0%) for personal history of BBD regarding non-behavioral factors and 5.1% (2.0 to 8.2%) for BMI, 5.4% (0.5 to 10.3%) for number of children and age at FFTP, 5.6% (1.9 to 9.3%) for alcohol consumption, 10.1% (2.6 to 17.4%) for dietary pattern, 14.5% (9.2 to 19.6%) for use of MHT (restricted to a combination of systemic oestrogen with a progestagen: 13.8% (10.1 to 17.4%), data not shown) and 17.1% (9.7 to 24.3%) for body shape at menarche regarding behavioral factors.

Population-attributable fractions of combinations of several risk factors

Proportions of premenopausal breast cancers attributable to the combination of all risk factors did not reach statistical significance (76.6% (−69.5 to 99.4%)), neither did non-behavioral factors [61.2% (−15.5 to 91.9%)] and behavioral factors [39.9% (−71.0 to 93.9%)] taken together (Table 3).

Table 3. Individual and combined PAFs associated with breast cancer risk factors for premenopausal and postmenopausal breast cancer, E3N cohort ($N = 67,634$)

	Premenopausal $N = 497$ PAF (95%CI)	Postmenopausal $N = 3,138$ PAF (95%CI)
Non-behavioral factors		
First-degree family history of breast cancer (ref = none)	2.44 (−0.37 to 5.25)	**3.64 (2.46 to 4.81)**
Level of education (ref = undergraduate)	8.82 (−22.70 to 38.63)	2.67 (−8.15 to 13.43)
Height at adulthood (ref = less than 160 cm)	4.87 (−13.30 to 22.69)	5.03 (−1.81 to 11.82)
History of benign breast disease (ref = none)	**14.11 (5.85 to 22.18)**	**14.85 (11.64 to 18.03)**
Age at menarche (ref = more than 14)	**19.81 (5.20 to 33.58)**	**9.70 (3.87 to 15.47)**
Birth weight (ref = low)	**33.58 (5.72 to 56.59)**	8.52 (−3.92 to 20.69)
Age at menopause, for postmenopausal women only (ref = less than 48)		7.37 (−1.67 to 16.29)
Combination of all non-behavioral factors	61.22 (−15.50 to 91.88)	**41.87 (4.97 to 68.71)**
Behavioral factors		
Tobacco smoking (ref = never)	5.06 (−5.24 to 15.26)	0.32 (−3.44 to 4.07)
Number of children and age at FFTP (ref = more than one child, the first before 30)	5.24 (−6.37 to 16.71)	**5.36 (0.45 to 10.25)**
Physical activity level (ref = highly active)	−0.40 (−20.60 to 19.82)	1.89 (−5.39 to 9.16)
Body shape at menarche (ref = body shape ≥ 4)	14.09 (−4.28 to 31.53)	**17.10 (9.73 to 24.30)**
Breastfeeding (ref = more than 6 months)	1.91 (−21.80 to 25.35)	4.09 (−5.15 to 13.26)
Dietary pattern (ref = high Healthy score and low Western score)	10.66 (−9.35 to 29.84)	**10.06 (2.64 to 17.36)**
Alcohol consumption (ref = less than one drink a day)	−0.25 (−9.36 to 8.87)	**5.62 (1.91 to 9.31)**
Vitamin D intake and UVRd (ref = high levels for both)	−0.16 (−20.10 to 19.81)	5.84 (−2.07 to 13.68)
Oral contraceptive or progestagen alone use (ref = last use more than 10 years ago or never used)	3.32 (−11.80 to 18.32)	3.52 (−1.32 to 8.34)
Body mass index (ref = more than 25 (premenopausal) or less than 25 (postmenopausal))	10.03 (−7.60 to 27.06)	**5.07 (1.97 to 8.16)**
Recent MHT use, for postmenopausal women only (ref = no recent MHT)		**14.46 (9.22 to 19.61)**
Combination of all behavioral factors	39.86 (−71.00 to 93.92)	**53.45 (12.81 to 78.72)**
Combination of all factors	76.64 (−69.50 to 99.37)	**72.88 (17.62 to 93.21)**

HRs were adjusted on age (as the time scale), first-degree family history of breast cancer, level of education, height at adulthood, history of benign breast diseases, age at menarche, birth weight, age at menopause (for postmenopausal women only), tobacco smoking, number of children and age at FFTP, physical activity level, body shape at menarche, breastfeeding, dietary pattern, alcohol consumption, vitamin D intake and UVRd, oral contraceptives or progesterone alone use, body mass index and menopausal hormone therapy use (for postmenopausal women only).

When limiting the estimation to the three factors that yielded a significant PAF in premenopause (history of benign breast disease, age at menarche and birthweight), a statistically significant percentage of premenopausal breast cancers were attributable to their combination [54.21% (13.16 to 79.39%), data not tabulated].

Regarding postmenopausal analyses, 72.9% (17.6 to 93.2%) of postmenopausal breast cancers could be attributable to the combination of all the considered variables. This percentage was 41.9% (5.0 to 68.7%) and 53.5% (12.8 to 78.7%) for the combination of the non-behavioral factors and the behavioral factors, respectively (Table 3). When limiting the estimation to all factors that yielded a significant PAF (first-degree family history of breast cancer, history of benign breast disease and age at menarche for non-behavioral factors; physical activity level, breastfeeding, dietary pattern, alcohol consumption and body mass index for behavioral factors), statistically significant percentages of postmenopausal breast cancers attributable to the combination of these non-behavioral and behavioral factors were found, equal to 25.84% (16.64 to 34.59%) and 43.36% (19.60 to 62.31%), respectively (data not tabulated).

Population-attributable fractions for premenopausal breast cancer according to hormonal receptors status

During follow-up, 314 premenopausal women were diagnosed with ER+ and 97 with ER- breast cancer. Due to low numbers, HER2 status could not be considered. Baseline characteristics and multivariate-adjusted HR with 95% CI among premenopausal women are available in Supporting Information Table 1.

Table 4. Individual and combined PAFs associated with breast cancer risk factors for ER+ and ER− premenopausal and postmenopausal breast cancer, E3N cohort ($N = 67,634$)

	Premenopausal breast cancer		Postmenopausal breast cancer	
	ER+ $N = 314$	ER− $N = 97$	ER+ $N = 2,050$	ER− $N = 466$
Non-behavioral factors	PAF		PAF	
First-degree family history of breast cancer (ref = none)	−0.26	5.82	**4.25**[1]	2.20
Level of education (ref = undergraduate)	5.33	−19.00	6.45	4.73
Height at adulthood (ref = less than 160 cm)	7.91	−26.20	**8.70**[1]	−0.35
History of benign breast disease (ref = none)	**16.21**[1]	11.79	**14.51**[1]	**15.31**[1]
Age at menarche (ref = more than 14)	14.14	**38.62**[1]	**14.47**[1]	3.51
Birth weight (ref = low)	21.37	**61.01**[1]	5.81	24.63
Age at menopause, for postmenopausal women only (ref = less than 48)	–	–	**12.83**[1]	−7.53
Combination of all non-behavioral factors	52.18	70.32	**50.82**[1]	38.07
Behavioral factors				
Tobacco smoking (ref = never)	8.87	−1.14	−0.20	1.80
Number of children and age at FFTP (ref = more than one child, the first before 30)	4.84	11.16	**7.05**[1]	−6.95
Physical activity level (ref = highly active)	−4.31	12.69	3.08	−0.34
Body shape at menarche (ref = body shape ≥ 4)	9.66	13.03	**15.25**[1]	6.82
Breastfeeding (ref = more than 6 months)	2.26	−1.43	7.82	−0.65
Dietary pattern (ref = high Healthy score and low Western score)	12.64	14.72	**12.85**[1]	7.82
Alcohol consumption (ref = less than one drink a day)	−0.92	−6.45	3.60	8.48
Vitamin D intake and UVRd (ref = high levels for both)	3.57	−10.90	8.50	4.64
Oral contraceptive or progestagen alone use (ref = last use more than 10 years ago or never used)	5.91	−1.08	3.81	2.17
Body mass index (ref = more than 25 (premenopausal) or less than 25 (postmenopausal))	**25.01**[1]	−12.40	**6.47**[1]	−1.05
Recent MHT use, for postmenopausal women only (ref = no recent MHT)	–	–	**17.51**[1]	5.00
Combination of all behavioral factors	50.56	21.80	**59.81**[1]	25.28
Combination of all factors	76.30	76.83	**80.21**[1]	53.61

HRs were adjusted on age (as the time scale), first-degree family history of breast cancer, level of education, height at adulthood, history of benign breast diseases, age at menarche, birth weight, age at menopause (for postmenopausal women only), tobacco smoking, number of children and age at FFTP, physical activity level, body shape at menarche, breastfeeding, dietary pattern, alcohol consumption, vitamin D intake and UVRd, oral contraceptives or progesterone alone use, body mass index and menopausal hormone therapy use (for postmenopausal women only).
[1] p values < 0.05.

PAFs corresponding to ER+ and ER− status are presented in Table 4 and in Supporting Information Table 5).

As many as 3 out of 4 cancers were attributed to the combination of all risk factors for each stratum. This result was driven by BMI [25.0% (3.8 to 44.1%)] and personal history of breast cancer [16.2% (5.6 to 26.5%)] for ER+ cancers and by birth weight [61.0% (17.6 to 84.6%)] and age at menarche [38.6% (6.1 to 63.7%)] for ER− cancers.

Population-attributable fractions for postmenopausal breast cancer according to hormonal receptors status

ER status was available for 2,516 postmenopausal breast cancers, HER2 status for 925 cancers and both statuses for 912 cancers; the distribution of cases is provided in Table 4. Baseline characteristics and multivariate-adjusted HR with 95% CI among postmenopausal women were available in Supporting Information Tables 1–4. PAFs are presented in Tables 4 and 5, and in Supporting Information Tables 6 and 7.

As many as 80.2% (20.3 to 96.4%) of postmenopausal ER+ cancers and 53.6% (−91.6 to 99.2%) of ER- cancers could be attributable to the combination of all considered variables. Statistically significant PAFs observed for all postmenopausal women were confirmed for ER+ cancers, with additional statistically significant PAFs for height at adulthood [8.7% (0.3 to 16.9%)] and age at menopause [12.8% (2.0 to 23.3%)]. Only one PAF remained statistically

Table 5. Individual and combined PAFs associated with breast cancer risk factors for several types of postmenopausal breast cancer, E3N cohort ($N = 67,634$)

	Postmenopausal breast cancer					
	HER2+ $N = 178$	HER2− $N = 747$	ER+/HER2+ $N = 113$	ER+/HER2− $N = 629$	ER−/HER2+ $N = 63$	ER−/HER2− $N = 107$
Non-behavioral factors	PAF			PAF		
First-degree family history of breast cancer (ref = none)	0.09	**4.26**[1]	4.23	**4.14**[1]	−7.19	6.24
Level of education (ref = undergraduate)	−26.00	**25.54**[1]	−20.90	**27.10**[1]	−24.70	9.36
Height at adulthood (ref = less than 160 cm)	19.35	12.71	27.51	13.11	7.94	14.72
History of benign breast disease (ref = none)	**16.55**[1]	**11.70**[1]	15.62	**10.91**[1]	16.06	15.75
Age at menarche (ref = more than 14)	5.47	9.72	2.21	11.91	14.58	−7.19
Birth weight (ref = low)	3.69	14.40	−12.20	11.73	28.38	23.12
Age at menopause, for postmenopausal women only (ref = less than 48)	**39.10**[1]	−1.52	40.69	4.60	34.23	−31.00
Combination of all non-behavioral factors	53.04	56.74	53.87	59.73	58.51	33.93
Behavioral factors						
Tobacco smoking (ref = never)	8.06	−0.68	11.16	−1.89	5.08	11.28
Number of children and age at FFTP (ref = more than one child, the first before 30)	−1.08	4.00	7.31	7.01	−18.30	−16.20
Physical activity level (ref = highly active)	−4.03	4.08	1.16	4.69	−17.10	−5.21
Body shape at menarche (ref = body shape ≥ 4)	8.72	**15.99**[1]	12.38	**19.85**[1]	0.11	−0.62
Breastfeeding (ref = more than 6 months)	4.48	15.15	3.77	14.02	5.33	17.36
Dietary pattern (ref = high Healthy score and low Western score)	3.59	**16.06**[1]	0.53	**16.56**[1]	12.09	13.81
Alcohol consumption (ref = less than one drink a day)	4.78	**9.54**[1]	8.22	8.94	0.62	14.23
Vitamin D intake and UVRd (ref = high levels for both)	−10.10	8.35	−15.00	8.28	2.59	14.15
Oral contraceptive or progestagen alone use (ref = last use more than 10 years ago or never used)	−4.69	2.11	−13.40	3.20	13.12	−5.60
Body mass index (ref = more than 25 (premenopausal) or less than 25 (postmenopausal))	12.21	**8.12**[1]	11.33	**10.45**[1]	13.33	−6.05
Recent MHT use, for postmenopausal women only (ref = no recent MHT)	0.63	**12.99**[1]	8.04	**15.00**[1]	−13.50	−0.55
Combination of all behavioral factors	22.39	63.91	33.75	68.00	11.42	36.07
Combination of all factors	63.57	84.33	69.46	87.08	63.00	57.78

HRs were adjusted on age (as the time scale), first-degree family history of breast cancer, level of education, height at adulthood, history of benign breast diseases, age at menarche, birth weight, age at menopause (for postmenopausal women only), tobacco smoking, number of children and age at FFTP, physical activity level, body shape at menarche, breastfeeding, dietary pattern, alcohol consumption, vitamin D intake and UVRd, oral contraceptives or progesterone alone use, body mass index and menopausal hormone therapy use (for postmenopausal women only).
[1] p values < 0.05.

significant for ER− cancers, obtained for personal history of BBD [15.3% (7.0 to 23.4%)]. The percentage of cancers attributable to all the considered variables for the other subtypes were estimated from 57.8% (−99.9 to 100%) for ER−/HER2− cancers to 87.1% (−25.7 to 99.4%) for ER+/HER2− cancers. The results for HER2− and ER+/HER2− cancers were similar to the overall analysis, except for age at menarche, parity and age at FFTP, and alcohol consumption for which the PAFs were no longer statistically significant. Regarding HER2+ cancers, only one PAF remained statistically significant, obtained for personal history of BBD [16.6% (3.0 to 29.5%)]. In addition, we observed statistically significant PAFs associated with level of education for HER2− [25.5% (4.7 to 4.2%)] and ER+/HER2− [27.1% (4.6 to 47.0%)] cancers and age at menopause for HER2+ [39.1% (6.2 to 64.3%)] cancers.

Sensitivity analyses

When excluding missing values or non-validated breast cancer cases or censoring breast cancer cases occurring within the first three years, non-behavioral risk factors were still associated with higher PAFs (from 59.5 to 77.7%) than behavioral risk factors (from 34.5 to 48.9%) in premenopause. The inverse was still observed in postmenopausal with higher PAFs for behavioral factors (from 49.4 to 58.0%) than for non-behavioral factors (from 38.3 to 45.2%). In these three sensitivity analyses, factors

associated with higher PAFs were the same in premenopause: personal history of BBD (from 14.0 to 14.9%), age at menarche (from 19.9 to 24.4%) and birth weight (from 33.0 to 53.8%). In postmenopause PAFs reaching the statistical significance in these three sensitivity analyses were those associated with family history of breast cancer (from 3.5 to 4.5%), BMI (from 5.0 to 6.5%), personal history of BBD (from 14.8 to 15.1%) and use of MHT (from 14.7 to 20.2%).

In postmenopause, BMI was associated with similar PAF when not adjusted on height at adulthood (5.1%), as alcohol consumption when not adjusted on smoking status or dietary pattern (4.6 and 5.6%, respectively), and dietary pattern when not adjusted on alcohol consumption (11.5%).

In premenopause, similar PAFs were observed for birth weight when adjusting models on length at birth (28.7%) or when considering premature babies as a separate category (35.2%).

Discussion

This article adds evidence to the literature that a high proportion of breast cancers can be avoided, both overall and in subgroups defined by tumour hormone receptor status.

To our knowledge, this is the first study to estimate combined PAFs associated with premenopausal and postmenopausal invasive breast cancer including an extended number of risk factors. The proportions of premenopausal breast cancers after 40 years of age that could be attributed to non-behavioral factors and to behavioral factors were not statistically significant, contrary to the proportions of postmenopausal breast cancers, for which the impact of behavioral factors was higher (54%) than non-behavioral factors (42%).

PAF is useful for comparing the population-level impacts of various risk factors on disease incidence. Because it is often misinterpreted, it must be specified that PAF associated with single risk factors cannot be summed to derive the combined PAFs associated with a combination of risk factors, and that combined PAF cannot be subtracted from 100% to determine the "unexplained" proportion of cases.[3] Furthermore, PAF estimates cannot be interpreted as the proportion of cases avoided if women were to change their behaviors but rather reflect comparisons between the observed distribution and hypothetical scenarios in which women were not exposed to the risk factors. At last, Spiegelman *et al.*[32] recommended using time-on-study instead of age as the time scale when estimating PAFs from Cox regression models. As time-on-study or age as the time scale provided similar results, Cox regression models using age as the time scale were used to avoid bias in HR estimates.[28]

Literature confrontation

To our knowledge, this is the first study to estimate PAFs associated with anthropometric measures around menarche and birth weight for premenopausal and postmenopausal breast cancer separately. One study[34] estimated the PAFs for overall breast cancer risk associated with BMI around menarche at 15% and with birth weight at 7%. Values of PAFs for body shape around menarche in our study were close for both premenopausal and postmenopausal breast cancer, although not statistically significant in premenopause. In addition, a high body shape score around menarche has previously been associated with a decreased risk of breast cancer in terms of HR.[35,36] Our results regarding birth weight are consistent with two recent meta-analyses showing a positive association between birth weight and breast cancer risk that was stronger in pre- than in post-menopausal women.[37,38]

Regarding premenopausal breast cancer, the statistically significant PAF observed in our analyses associated with a late menarche were consistent with recent published estimate of 22.2%.[7]

Regarding postmenopausal breast cancer, the individual PAF observed for MHT was within the range observed in the literature (2.4 to 19.4%).[6–8,11,39,40] The results suggested that a statistically significant number of postmenopausal breast cancer cases could be attributed to the recent use of MHT, restricted to a combination of systemic oestrogen with a progestagen.[17] The postmenopausal individual PAF observed for BMI was within the range noted in the literature (0.2 to 24.8%),[7–10,39–41] as were those for alcohol (−7.6 to 9.1%),[6–8,10,40] age at menopause (5.9 to 14.5%)[6–8,11] and age at menarche (7.7 to 18.8%)[5–8] The postmenopausal PAF associated with family history of breast cancer was lower than previously published estimations (5.7 to 15.7%)[5–9,11] because of a lower prevalence of family history in our study population (up to 20.4% in the literature *vs.* 7.3% in our population) and lower relative risk estimates (1.49 to 6.29 in the literature *vs.* 1.37 and 1.50 among premenopausal and postmenopausal women in our analyses, see Tables 1 and 2).

Few studies quantified the joint influence of behavioral and/or non-behavioral factors on premenopausal,[10,11] postmenopausal[6,8–11] and overall[5,7,12,13] breast cancer. Among them, very few jointly analyzed the impact of only behavioral factors,[6,8,10] only non-behavioral factors,[6,8,11] or their combination.[9,11] Previously published combined PAFs for premenopausal breast cancer were 42.8% of cases attributable to the combination of a high consumption of alcohol and a low level of physical activity,[10] and 52.0% of cases attributable to the combination of low level of education, having a child before 20 and having family history of breast cancer.[11]

For postmenopausal breast cancer, different combinations of behavioral risk factors were associated with PAFs of 26.3% (including physical activity, use of MHT, BMI and alcohol consumption),[8] 40.7% (including physical activity, use of MHT, alcohol consumption and weight gain since age 18 years)[6] and from 12.4 to 40.7% when combining two factors among alcohol consumption, physical activity and body mass index.[10] In our study, the observed PAF for behavioral risk factors (42.3%) was higher than these published estimates. Regarding non-behavioral risk factors, previously published PAFs were 37.2%[8] combining age at menopause, parity, BBD,

age at menarche and family history of breast and 57.3% when adding age at FFTP and height at adulthood to the estimation.[6]. In our study, we observed a PAF associated with non-behavioral factors of 51.7%. Differences found for both the combination of behavioral and non-behavioral factors may result from a higher number of factors included in our study.

Our results are in line with the only previously published study that evaluated individual and combined postmenopausal PAFs stratifying on hormonal receptor status,[8] in which the use of MHT, age at menopause and age at menarche were associated with higher PAF estimates for ER+ than ER- cancers.[8] In addition, previous pooled- and meta-analyses have found that a high BMI was associated with a decreased risk of ER+/PR+ premenopausal breast cancer in terms of HR[15] and that the decreased risk of postmenopausal breast cancer for a 5-unit increase in BMI was restricted to ER+/PR+ postmenopausal breast cancer.[15] Though not statistically significant, one study found that a late menarche was associated with a decreased risk of ER- premenopausal breast cancer and increased risk of ER+ premenopausal breast cancer.[42] A late menarche has previously been associated with a decreased risk of ER+[14,43] breast cancer. High BMI around menarche has been associated with a decreased risk of ER−,[44] ER+/PR−[45] and ER+/PR+[35] postmenopausal breast cancer. Use of MHT has been associated with an increased risk of ER+/PR+,[43] ER+[46] and HER2−[47] postmenopausal breast cancer.

Strengths and limitations

The cut-points used to define exposure levels can have an effect on PAFs estimates.[33] However to avoid bias, the categorization used had been chosen *a priori* and based on the literature and public health recommendations. Age and body shape at menarche were retrospectively collected from women aged 40–65 years at baseline and thus require long-term memory, which may generate measurement errors. However, an independent validation study showed that this information was reliable (correlations between original and recalled was 0.8 for age and 0.6 for body shape).[48] In addition, like most cohorts, the E3N population is not representative of the general population and is prone to a healthy cohort effect. As PAF estimates depend on the prevalence of exposures among the population of interest, PAF of healthy behaviors (non-smoking, high physical activity level, limiting alcohol or low BMI) would be higher in a less healthy population. However, assessing PAFs in the general population is not feasible because of the lack of data on their prevalence. If PAFs estimates are useful to rank risk factors, it is obvious that public health interventions are not possible for all (age at menarche for instance). Finally, limited number of premenopausal breast cancer cases were observed, resulting from the selection of the cohort population restricted to women over 40 years, where genetic factors are less predominant than in younger women.[49] Due to these low numbers of premenopausal cases, especially in the birthweight reference category, results for premenopausal women should be interpreted with caution.

The main strength of these analyses is the size of the cohort and an extended follow-up enabling a high statistical power and a wide set of available risk factors. The study design also enabled analysis of the heterogeneity of subgroups of breast cancer defined by its menopausal and receptor status. Histological confirmation was obtained for the vast majority of breast cancer cases, and exclusion of non-validated cases produced similar results. Because of the prospective design, information on exposure collected prior to cancer diagnosis resulted in low risk of recall bias. In addition, dietary and anthropometric data were validated,[21,50] and demonstrated limited declaration bias and good reliability of the reported data. Another strength is the formula used to estimate the PAF, allowing a non-biased estimation of adjusted PAF.[3]

Conclusions

Never adopted unhealthy behaviors could have a large impact on postmenopausal breast cancer risk. Health agencies should favour more effective information on the most important behavioral factors for breast cancer: alcohol consumption, diet, postmenopausal obesity and menopausal hormone therapy and encourage research on how to modify people's behaviors.

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