Use of hormones in the menopausal transition period in the Netherlands between 1993 and 1997

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Abstract

Objectives: To describe the patterns and to assess the indicators of hormone use during the menopausal transition period in a Dutch population.

Methods: Between 1993 and 1997, 17,357 women aged 49–70 years participated in the Prospect-EPIC (European Prospective Investigation into Cancer and Nutrition) cohort and filled out an extensive questionnaire, which included information about hormone use during menopausal transition and other medical and lifestyle characteristics. Patterns of hormone use were described and various characteristics were evaluated as indicators of current hormone use by logistic regression.

Results: Overall, 13% of women were current hormone users, which was highest in the 49–54 age group (19%). Hysterectomized women and older non-hysterectomized women mainly used unopposed estrogen therapy (ET), whereas younger non-hysterectomized women mainly used oral contraceptives or combined estrogen + progestogen therapy. Of all ever users, 61% used hormones for more than 1 year and 28% for more than 5 years.

The most important indicators of hormone use for women without a surgical menopause were age, alcohol use, smoking, parity, ever use of oral contraceptives and family history of breast cancer. For women with a surgical menopause age, parity, ever use of oral contraceptives, diastolic blood pressure and the number of removed ovaries were the most relevant indicators.

Conclusions: The frequency of hormone use during menopausal transition in the Netherlands is low compared to other western countries, but the duration of use is quite long. Hormone use seems to be largely determined by factors that are known to affect endogenous estrogen levels.

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1. Introduction

For alleviation of climacteric problems hormone use is mainly prescribed [1]. There is, however, marked discussion on the side effects of some types of hor-

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mones that are used. Women who use hormone therapy (HT) appear to have an increased risk of breast cancer [2–4]. Furthermore, although HT was thought to have a beneficial effect on cardiovascular disease according to several observational studies [5], these findings have not been supported by results from randomized clinical trials [6–8]. On the contrary, the results of the most recent trial even suggest an increased risk of cardiovascular disease due to HT use [8].

In order to estimate the impact of the effects of HT in a population, several issues have to be taken into account. On a population level, the impact of potential HT effects depends on the proportion of women who use HT. This proportion varies widely between western countries: HT prescription is highest in Australia, followed by the United States, France and the United Kingdom. Other European countries on the continent have the lowest usage [9]. However, the proportion of women in European countries who use HT has increased over the last two decades [10,11].

Also relevant are the many different types of HT regimen that are prescribed, which may have different effects on disease risk. The first generation hormone preparations have been prescribed since the end of the 1960s and comprise estrogens only, but in most studies these show an increased risk of breast cancer [2,12] and especially endometrial cancer [13]. Combined HT, where progestogen is added to estrogen, has been prescribed since the early 1990s, because it reduces the incidence of endometrial hyperplasia and probably endometrial cancer associated with the use of estrogen alone [14]. However, the addition of progestogen increases the risk of breast cancer more than estrogen alone [15]. Tibolone, a synthetic drug that has weak estrogenic, progestagenic and androgenic activity appeared in 1987 on the Dutch market and is also used to relieve menopausal complaints. It has been associated with an inhibitory effect on both tumor growth and proliferation rates in normal human epithelial breast cells [16], but nevertheless it has also been shown to increase the risk of breast cancer [12].

For each type of menopausal hormone use, the composition of HT may differ according to period and place. Many observational studies and trials have been performed in the United States, where conjugated equine estrogens are the most widely prescribed preparation of unopposed estrogen therapy (ET) [17]. In most European countries, however, ET consists of estradiol or one of its esters. The composition of combined HT also varies widely within and between countries, both in the type of estrogens and type of progesterons used [18,19].

The effects of HT may also depend on the population studied. HT users in observational studies may differ greatly from those included in clinical trials, the latter often being without menopausal complaints. In practice, HT users generally have menopausal complaints caused by a fall in estrogen levels, which may result in different effects of HT [20–22]. Besides that, HT users seem to have other medical, socio-economic and lifestyle characteristics than women who do not use HT [10,23,24]. Characteristics such as previous oral contraceptive use, smoking, alcohol use, higher education and a history of gynaecological surgery have been shown to be more frequent and characteristics such as a high body mass index (BMI) and a medical history of breast cancer or diabetes mellitus have been shown to be less frequent in HT users compared to non HT users. These characteristics have not yet been determined in a large cohort study in the Netherlands.

In the present study, we describe the distribution, type of regimen and duration of HT use and we assess the indicators of HT use in Dutch women aged 49–70 years between 1993 and 1997, separately for surgical and non-surgical menopausal women.

2. Methods

2.1. Study population

This study is a cross-sectional study, using the baseline data from the Prospect-EPIC study [25], a Dutch cohort in the European Prospective Investigation into Cancer and Nutrition (EPIC) [26]. Between 1993 and 1997, 17,357 women were recruited through an existing regional population-based program of breast cancer screening for enrollment in the Prospect-EPIC study. Participants were between 49 and 70 years of age and were living in Utrecht and surroundings.

2.2. Questionnaire data

Data for this study were obtained on the basis of a medical examination and a self-administered questionnaire, which among others included questions

on socio-demographic and lifestyle factors, reproductive factors, medical history and HT use. HT use was defined as the use of hormones for menopausal complaints, which for completeness also included oral contraceptives used for menopausal complaints. The questionnaire comprised questions on the age at which women started and stopped using HT. Current HT users are defined as those women who reported that they were using HT when they completed the questionnaire and past HT users were women who reported that they had used HT in the past, but had discontinued. For current users information on the type of HT regimen was gathered by registration of medication boxes, which women were asked to bring to the breast screening examination at inclusion. We distinguished ET, combined HT, in which progestogen is used in addition to estrogen, tibolone, oral contraceptives for menopausal complaints or the use of other hormone types. The category combined HT consists of sequential preparations, continuous preparations and combinations of estrogen and progestogen in which they are given as two separate preparations. The other hormone types include preparations of only progestagens or preparations with anti-androgens.

Information on potential indicators of HT use was obtained through the questionnaire and medical examination. A validated food frequency questionnaire, which was developed to estimate the usual frequency of consumption of different food and beverage items over the preceding 12 months, was also used in order to obtain information on current alcohol consumption [27,28]. Potential indicators include age at recruitment, education, lifestyle factors, reproductive factors and medical information.

Age at recruitment was categorized as 49–54, 55–59, 60–64 and 65–70 years. The highest completed education that women reported was divided in four categories: primary education, vocational or advanced elementary education, higher secondary education and university.

2.2.1. Lifestyle factors

Current alcohol intake was defined as grams of ethanol per day and one glass of any alcoholic beverage was assumed to contain 10 g of alcohol. The alcohol intake of women who consumed less than 1 g/day was set to zero. The alcohol consumption was then classified into three categories: 0, 1–10 and >10 g/day.

Smoking was categorized as 0, <5, 5–15 and >15 pack years. Pack years was defined as the mean number of cigarettes per day divided by 25 and multiplied by years of smoking. Physical activity was assessed using the Voorrips-questionnaire, which consists of scores in household, sporting and recreational activities and is validated in an elderly female population [29]. The Voorrips scores were categorized in quartiles, where the lowest category represents lowest physical activity.

2.2.2. Reproductive factors

Age at menarche was categorized in quartiles. Parity was divided in five categories: no children, one child, two children, three children and four or more children. Oral contraceptive use was defined as the use of oral contraceptives for reasons other than menopausal complaints and was categorized as never and ever. When women use hormone replacement therapy, which is usually started during perimenopause, the status of natural menopause [30,31] and age at natural menopause is difficult to establish and these variables were, therefore, not included in the analyses. The variable ovariectomy was divided in three categories: no ovariectomy, unilateral ovariectomy and bilateral ovariectomy.

2.2.3. Medical information

BMI was categorized as <20, $\geq$20 and <25, $\geq$25 and <30, $\geq$30 and <35, and $\geq$35 kg/m^2. Diastolic and systolic blood pressures (mmHg) were measured twice and results were averaged and categorized in quartiles. Family history of breast cancer, defined as at least a mother or a sister diagnosed with breast cancer, and ever having had cancer, heart attack, stroke and diabetes mellitus was self-reported and categorized as no and yes.

2.3. Data analysis

The distribution of HT use (current, past, never users) was compared between 5-year age groups. Among current users the type of regimen was assessed by 5-year age group. The type of regimen that is prescribed is expected to depend on whether or not a woman still has a uterus, because of the findings that the use of estrogens alone increases the risk of endometrial cancer. Therefore, these analyses were carried out separately for hysterectomized and

non-hysterectomized women. Duration of HT use was assessed for ever users in four categories: 1 year or less, 2–4 years, 5–9 years and 10 years or more. These analyses were done separately for women with a surgical menopause, where surgical menopause was defined as having had an ovariectomy and/or a hysterectomy, and for women without a surgical menopause, which also includes premenopausal women.

To identify indicators of current HT use, odds ratios (OR) and 95% confidence intervals for the relationships between age, education, lifestyle, reproductive and medical characteristics on the one hand and current HT use on the other hand were estimated. The current HT group consisted of women who used ET, combined HT, tibolone, oral contraceptives for menopausal complaints or other hormones for menopausal complaints. A multivariate logistic regression model was built, starting with all selected variables and allowing, after backward selection, only variables with p-value <0.10 in the final model. The indicators of current HT use are expected to be different for women with a surgical menopause than for women without a surgical menopause, because the first group has a medical indication for their HT use. Therefore, the univariate as well as the multivariate analyses were carried out separately for women with and without a surgical menopause. Due to missing values 1075 women (6.2%) were excluded from the multivariate models.

Statistical analyses were performed with SPSS version 11.5.

3. Results

Overall, 13.2% of women reported to be current users and 12.2% of women reported to be past users of HT (Table 1). Current use of HT was highest (19.4%) in the 49–54 age group and declined from 14.7% in the 55–59 age group to 6.8% in the 60–65 age group and 2.7% in the 65–70 age group. The proportion of never users was larger among older women (85.3%) than among younger women (69.5%).

For 1817 out of the 2256 current HT users, the exact HT preparation was known (Table 2). The type of regimen of HT that was taken by current users was strongly dependent on whether a woman was hysterectomized and on age. Hysterectomized women mainly used ET (74.1%). Combined HT was used by 2.3%, tibolone by 3.2% and both oral contraceptives for menopausal complaints and other types of hormones by 0.5% of hysterectomized women. Among hysterectomized women no differences in type of HT use were observed between age groups. In the non-hysterectomized group, younger women (49–54 age group) were most likely to use oral contraceptives (27.1%) for their menopausal complaints, closely followed by combined HT (24.4%) and ET (17.0%). Older women (65–70 age group) were most likely to use ET (36.4%).

When the composition of each hormone preparation was assessed, it was found that most ET consisted of estradiol (65.2%) followed by conjugated estrogens (26.5%), estriol (6.1%) and ethinylestradiol (2.1%). The progestogens in combined HT were testosterone derivatives (68.9%), progesterone derivatives (30.0%) or progesterone (1.0%) in combination with various kinds of estrogens. The oral contraceptives for menopausal complaints consisted of estrogens with levonorgestrel (38.1%), medroxyprogesterone (31.7%), desogestrel (17.2%), gestodeen (11.1%) or other compounds (2.0%) (data not shown).

Table 1
Hormone use by 5-year age group in 1993–1997

HT use	Age group				Total	
	49–54% (S.E.[a])	55–59% (S.E.)	60–64% (S.E.)	65–70% (S.E.)	%	N
Current	19.4 (0.5)	14.7 (0.6)	6.8 (0.4)	2.7 (0.3)	13.2	2256
Past	11.1 (0.4)	14.8 (0.6)	11.5 (0.5)	12.0 (0.6)	12.2	2086
Never	69.5 (0.5)	70.5 (0.7)	81.7 (0.7)	85.3 (0.7)	74.6	12786
Total (%)	100.0	100.0	100.0	100.0	100.0	
Total N	7086	3930	3437	2675		17128

[a] S.E., standard error of the mean.

Table 2
Current HT use by type of HT and 5-year age group

Type of HT	Hysterectomy				Subtotal	
	49–54% (S.E.[c])	55–59% (S.E.)	60–64% (S.E.)	65–70% (S.E.)	%	N
Combined HT	2.1 (0.7)	2.1 (0.9)	4.2 (1.8)	–	2.3	20
ET	76.2 (1.9)	73.6 (2.9)	66.9 (4.3)	71.8 (7.2)	74.1	652
Tibolone	3.3 (0.8)	3.3 (1.2)	1.7 (1.2)	5.1 (3.5)	3.2	28
Oral contraceptives	0.4 (0.3)	0.4 (0.4)	–	2.6 (2.5)	0.5	4
Other[a]	0.4 (0.3)	0.8 (0.6)	–	–	0.5	4
Unknown	17.6 (1.7)	19.7 (2.6)	27.1 (4.1)	20.5 (6.5)	19.5	172
Total (%)	100.0	100.0	100.0	100.0	100.0	
Total N	484	239	118	39		880
Median duration of use in years (IQR[b])	3.0 (2.0–5.0)	6.0 (3.0–10.0)	8.5 (5.0–13.0)	14.5 (7.5–19.3)	4.0 (2.0–9.0)	

Type of HT	No hysterectomy				Subtotal		Total	
	49–54% (S.E.[c])	55–59% (S.E.)	60–64% (S.E.)	65–70% (S.E.)	%	N	%	N
Combined HT	24.4 (1.4)	33.0 (2.6)	24.1 (4.0)	18.2 (7.1)	26.4	363	17.0	383
ET	17.0 (1.3)	26.3 (2.4)	32.8 (4.4)	36.4 (8.4)	21.1	290	41.8	942
Tibolone	6.1 (0.8)	11.2 (1.7)	12.1 (3.0)	15.2 (6.2)	8.1	111	6.2	139
Oral contraceptives	27.1 (1.5)	10.6 (1.7)	12.1 (3.0)	6.1 (4.2)	21.3	293	13.2	297
Other[a]	4.7 (0.7)	1.5 (0.7)	4.3 (1.9)	–	3.8	52	2.5	56
Unknown	20.6 (1.4)	17.4 (2.1)	14.7 (3.3)	24.2 (7.5)	19.4	267	19.5	439
Total (%)	100.0	100.0	100.0	100.0	100.0		100.0	
Total N	888	339	116	33		1376		2256
Median duration of use in years (IQR[a])	2.0 (1.0–4.0)	4.0 (2.0–6.0)	6.5 (3.0–10.0)	8.0 (3.0–15.0)	3.0 (1.0–5.0)		3.0 (2.0–6.0)	

[a] Includes preparations of progestogen only or preparations with anti-androgens.

[b] IQR, inter-quartile range.

[c] S.E., standard error of the mean.

Table 3
Duration of hormone therapy in ever users

Duration of HT	Surgical menopause % (S.E.[b])	No surgical menopause % (S.E.)	Total	
			%	N
One year or less	31.0 (1.2)	43.6 (1.0)	39.0	1593
2–4 years	31.8 (1.2)	34.0 (0.9)	33.2	1357
5–9 years	19.8 (1.0)	16.9 (0.7)	17.9	733
10+ years	17.4 (1.0)	5.5 (0.4)	9.8	402
Total (%)	100.0	100.0	100.0	
Total N	1494	2591		4085
Median duration in years (IQR[a])	3.0 (1.0–7.0)	2.0 (1.0–4.0)	2.0 (1.0–5.0)	
Median age start (IQR)	49.0 (45.0–51.0)	50.0 (47.0–52.0)	49.0 (47.0–52.0)	

[a] IQR, inter-quartile range.
[b] S.E., standard error of the mean.

Data on duration of HT use were available for 97% of ever users, which includes current and past users, as presented in Table 3. The duration of use in ever users ranged from less than 1 year to 30 years. Of all ever users, 61.0% used HT for more than 1 year and 27.7% used HT for more than 5 years. The median duration of use was 2.0 years and the median age of start was 49.0 years. Women with a surgical menopause were shown to have a higher median duration (3.0 years) than women without a surgical menopause (2.0 years) and to have a younger median age at start (49.0 years) than women without a surgical menopause (50.0 years).

Characteristics associated with current use of HT in univariate and multivariate models for women with and without a surgical menopause are shown in Tables 4a and 4b.

Among women without a surgical menopause older women were less likely to report the use of HT. Women who had a higher education than primary education were more likely to be current HT users. Women who drink more alcohol and have smoked more pack years were more likely to be current HT users. Physical activity was not associated with current HT use. Earlier menarche was associated with higher HT use. The relation with parity was n-shaped, with the highest use in the categories for one to two children. Current HT use was more frequent among women who ever used oral contraceptives for reasons other than menopausal complaints.

Women with a higher BMI or with a higher systolic blood pressure as well as women with a family history of breast cancer or women who reported to ever have

had a heart attack or to be diabetic were less likely to use HT. No association was found between diastolic blood pressure, self-reported stroke or self-reported cancer and current use of HT.

In the multivariate model age at recruitment, alcohol use, smoking, number of children, oral contraceptive use and family history of breast cancer were independent predictors of current HT use for women without a surgical menopause.

Among women with a surgical menopause the frequencies of current HT use according to age, education, lifestyle characteristics, reproductive factors and medical characteristics were broadly similar to those among women without a surgical menopause. The differences were that physical activity was positively associated, diastolic blood pressure was negatively associated and age at menarche, family history of breast cancer, self-reported heart attack and self-reported diabetes mellitus were not associated with current HT use in women with a surgical menopause. Women with an ovariectomy were also more likely to report current HT use in this group.

In the multivariate model age at recruitment, number of children, oral contraceptive use, diastolic blood pressure and the number of removed ovaries were independent predictors of current HT use for women with a surgical menopause.

The potential indicators from Tables 4a and 4b were also assessed in relation to ever HT use instead of current HT use. In women without a surgical menopause, all characteristics showed odds ratios in a similar direction (data not shown). In the surgical menopause group women with a unilateral ovariec-

Table 4a

Possible indicators of current use of hormone therapy in women without a surgical menopause

Characteristic	Univariate		Multivariate	
	OR	95% confidence interval	OR	95% confidence interval
Age at baseline (years)				
49–54	1 (reference)		1 (reference)	
55–59	0.71	0.62–0.81	0.80	0.69–0.93
60–64	0.26	0.21–0.32	0.33	0.26–0.40
65–70	0.08	0.05–0.12	0.10	0.07–0.16
Education				
Primary	1 (reference)			
Vocational or advanced elementary	1.48	1.25–1.76		
Higher secondary	1.90	1.49–2.42		
University	1.72	1.41–2.09		
Lifestyle factors				
Current alcohol intake (g/day)				
0	1 (reference)		1 (reference)	
1–10	1.37	1.17–1.60	1.13	0.96–1.33
>10	1.84	1.58–2.15	1.33	1.13–1.56
Smoking (pack years)				
0	1 (reference)		1 (reference)	
<5	1.36	1.15–1.61	1.13	0.95–1.35
5–15	1.67	1.43–1.95	1.33	1.13–1.57
>15	1.67	1.44–1.95	1.39	1.18–1.63
Voorrips score				
≤2.69	1 (reference)			
>2.69–5.41	1.15	0.96–1.37		
>5.41–9.36	1.10	0.92–1.31		
>9.36	1.18	1.00–1.41		
Reproductive factors				
Age at menarche				
≤12	1 (reference)			
13	0.87	0.74–1.02		
14	0.89	0.76–1.05		
≥15	0.77	0.65–0.91		
Parity (number of children)				
0	1 (reference)		1 (reference)	
1	1.31	1.02–1.67	1.13	0.88–1.46
2	1.43	1.20–1.72	1.18	0.98–1.43
3	0.95	0.77–1.17	0.93	0.75–1.16
≥4	0.47	0.36–0.61	0.71	0.54–0.93
Oral contraceptive use ever				
No	1 (reference)		1 (reference)	
Yes	2.02	1.76–2.32	1.19	1.03–1.39
Medical information				
BMI (kg/m^2)				
<20	1 (reference)			
≥20 and <25	1.04	0.71–1.52		
≥25 and <30	0.88	0.60–1.28		
≥30 and <35	0.71	0.47–1.07		
≥35	0.49	0.28–0.85		

Table 4a (*Continued*)

Characteristic	Univariate		Multivariate	
	OR	95% confidence interval	OR	95% confidence interval
Diastolic blood pressure (mm Hg)				
<73	1 (reference)			
73–79	0.94	0.80–1.11		
80–86	0.95	0.81–1.11		
≥87	0.86	0.73–1.01		
Systolic blood pressure (mm Hg)				
<120	1 (reference)			
120–131	0.88	0.76–1.03		
132–144	0.71	0.60–0.83		
≥145	0.66	0.56–0.78		
Cancer ever				
No	1 (reference)			
Yes	0.93	0.71–1.24		
Family breast cancer				
No	1 (reference)		1 (reference)	
Yes	0.73	0.60–0.88	0.82	0.67–1.00
Heart attack				
No	1 (reference)			
Yes	0.39	0.18–0.82		
Stroke				
No	1 (reference)			
Yes	0.87	0.53–1.44		
Diabetes Mellitus				
No	1 (reference)			
Yes	0.44	0.27–0.73		

tomy were less likely to report current HT use, whereas women with a bilateral ovariectomy were more likely to report current HT use compared to women with no ovariectomy. All other characteristics showed odds ratios in a similar direction (data not shown).

Multivariate models were also assessed in relation to ever HT use instead of current HT use. In the model for women without a surgical menopause, systolic blood pressure was included as an independent predictor, but family history of breast cancer was no longer an independent predictor.

In the model for women with a surgical menopause, education, alcohol use and diabetes mellitus were retained in the model and diastolic blood pressure was dropped from the model. The other variables were the same as in the multivariate models for current HT use and showed odds ratios in a similar direction (data not shown).

4. Discussion

In the Prospect-EPIC study 13% of women were current HT users. Of ever users, 61% used HT for more than 1 year and 28% used HT for more than 5 years. Many characteristics were related to current HT use, of which age, alcohol use, smoking, parity, oral contraceptive use and family history of breast cancer were the most important indicators for women without a surgical menopause. For women with a surgical menopause age, parity, oral contraceptive use, diastolic blood pressure and the number of removed ovaries were the most important indicators.

The percentage of current HT users in our cohort is low compared to other countries such as Australia, where 42% of women is using HT, the United States where 38% of women is using HT or France where 37% of women is taking HT [9]. One may argue that the percentage of HT use found in the Prospect-EPIC

Table 4b

Possible indicators of current use of hormone therapy in women with a surgical menopause

Characteristic	Univariate		Multivariate	
	OR	95% confidence interval	OR	95% confidence interval
Age at baseline (years)				
49–54	1 (reference)		1 (reference)	
55–59	0.63	0.53–0.75	0.68	0.56–0.81
60–64	0.32	0.26–0.40	0.36	0.29–0.46
65–70	0.14	0.10–0.19	0.16	0.11–0.22
Education				
Primary	1 (reference)			
Vocational or advanced elementary	1.47	1.22–1.76		
Higher secondary	1.70	1.25–2.32		
University	1.32	1.02–1.72		
Lifestyle factors				
Current alcohol intake (g/day)				
0	1 (reference)			
1–10	1.31	1.10–1.57		
>10	1.45	1.20–1.74		
Smoking (pack years)				
0	1 (reference)			
<5	1.32	1.07–1.64		
5–15	1.41	1.15–1.73		
>15	1.45	1.20–1.74		
Voorrips score				
≤2.69	1 (reference)			
>2.69–5.41	1.20	0.97–1.48		
>5.41–9.36	1.21	0.97–1.49		
>9.36	1.36	1.10–1.68		
Reproductive factors				
Age at menarche				
≤12	1 (reference)			
13	0.94	0.77–1.14		
14	0.92	0.75–1.13		
≥15	0.82	0.67–1.01		
Parity (number of children)				
0	1 (reference)		1 (reference)	
1	1.55	1.11–2.15	1.32	0.93–1.86
2	1.44	1.12–1.86	1.11	0.85–1.45
3	1.20	0.92–1.58	1.03	0.77–1.37
≥4	0.60	0.44–0.82	0.68	0.49–0.94
Oral contraceptive use ever				
No	1 (reference)		1 (reference)	
Yes	2.03	1.73–2.38	1.40	1.17–1.68
Medical information				
BMI (kg/m^2)				
<20	1 (reference)			
≥20 and <25	1.28	0.72–2.27		
≥25 and <30	1.00	0.56–1.77		
≥30 and <35	0.91	0.50–1.64		
≥35	0.59	0.29–1.20		

Table 4b (*Continued*)

Characteristic	Univariate		Multivariate	
	OR	95% confidence interval	OR	95% confidence interval
Diastolic blood pressure (mm Hg)				
<73	1 (reference)		1 (reference)	
73–79	0.87	0.71–1.07	0.87	0.70–1.07
80–86	0.87	0.72–1.06	0.87	0.70–1.06
≥87	0.70	0.57–0.86	0.71	0.58–0.88
Systolic blood pressure (mm Hg)				
<120	1 (reference)			
120–131	0.86	0.70–1.04		
132–144	0.71	0.58–0.87		
≥145	0.59	0.48–0.73		
Cancer ever				
No	1 (reference)			
Yes	0.84	0.65–1.07		
Family breast cancer				
No	1 (reference)			
Yes	0.83	0.66–1.04		
Heart attack				
No	1 (reference)			
Yes	0.63	0.36–1.09		
Stroke				
No	1 (reference)			
Yes	1.07	0.63–1.81		
Diabetes Mellitus				
No	1 (reference)			
Yes	0.72	0.47–1.09		
Ovariectomy				
No	1 (reference)		1 (reference)	
Unilateral	1.44	1.23–1.69	0.85	0.71–1.03
Bilateral	1.76	1.48–2.10	1.60	1.29–1.98

study does not reflect the percentage of HT use in the Netherlands, because the participants in this cohort choose to participate and are, therefore biased towards the use of HT. Another study on HT use in the Netherlands [32], however, was performed using a large pharmacy database, in which all medical prescriptions of a large part of the Netherlands are gathered and this study showed comparable results. In our study, the proportion of ever users declined with age, ranging from 31% in the 49–54 age group to 15% in the 65–70 age group. This indicates that the prescription rate of HT has increased over the years. This increase in HT users over the last years has been described in several other European studies [10,11].

Long-term users are at increased risk of breast cancer as has been reported in a variety of studies [2]. In our study, 28% of ever users took HT for more than 5 years (Table 3). Recently, the Million Women study [12] showed that even HT use for 1–4 years increases breast cancer risk. In our study, 33% of ever users had taken HT for 2–4 years, which together with long-term users (28%) results in at least 61% of users who may be at an increased risk of breast cancer.

The median duration of all HT users in this Dutch study was 2 years. These data do not correspond with an earlier study from Groeneveld et al. [33], who showed that the mean duration of HT use in Dutch women was only 7 months. In this study, 103 women, who started HT in 1990 or 1991, were followed for 2.25 years.

Only 15% of these women used HT for more than 1 year and 8% took HT for more than 2 years. When we, for comparison, included only women who started HT in 1990 or 1991, the median duration was 3 years. One possibility for this discrepancy may be that the study from Groeneveld was based on only 103 HT users. Furthermore, the composition of the study population is different than the population in our study, where all women were recruited through a breast cancer screening program. Another possibility is that the proportion of hysterectomized women in our study was higher than that in the former study. Recently, another study on the duration of HT use in a Dutch population was published [32], which showed that in 2002 74% of users took HT for more than 1 year and 37% of users took HT for more than 5 years. The percentage of users in that study was based on current users, whereas the percentage of users in our study was based on ever users, which may explain the fact that the percentage of women who took HT for more than 5 years is higher in that study (37%) than in our study (28%). Furthermore, the results of the study by Tobi et al. [32] were based on pharmacy data, whereas our results are based on questionnaire data, which may also explain the difference in results.

Among non-hysterectomized women, older women were most likely to use ET followed by combined HT and oral contraceptives for menopausal complaints, while younger women were most likely to use oral contraceptives for menopausal complaints, followed by combined HT and ET. This may indicate that the type of HT prescribed has changed over the years. Older women started their HT use already in the 1970s or 1980s, when ET was still the mostly prescribed therapy, and probably continued the use of the preparation they started with. The finding that ET use is much lower among younger (17%) than among older users (36%), probably reflects the knowledge that ET increases the risk of endometrial cancer and, therefore, was prescribed less frequently.

Furthermore, 13% of all current users took oral contraceptives for menopausal complaints, which was as high as 21% in the non-hysterectomized group. In the questionnaire, a distinction was made between this regimen for the use of contraception or for the relief of menopausal problems. Therefore, we can assume that these 13% of users indeed took oral contraceptives specifically for the relief of menopausal problems. The estrogens and progestagens in oral contraceptives are

structurally different chemicals than those in HT and are of higher potency [34], which may indicate that the risk of breast cancer and cardiovascular disease related to oral contraceptive use is different compared to other types of HT. Many groups have studied the relation between breast cancer risk and use of hormonal contraceptives and together these studies showed a small increase in breast cancer risk for women who are taking combined oral contraceptives and in the 10 years after stopping [35]. Furthermore, oral contraceptive use increases the risk of cardiovascular disease as is shown by several studies [36–38].

Most studies assessing effects of HT have been executed in the United States, where conjugated equine estrogens are the main component of ET and where conjugated equine estrogens together with medroxyprogesterone acetate (MPA), a progesterone derivative, are the main component of combined HT. In this study, however, ET consisted of estradiol for 65% of the women and conjugated estrogens for only 26% of the women, which is in agreement with the composition of ET in other European countries [17]. Furthermore, the progestogens in the combined HT regimens were testosterone derivatives for 69% of the women and progesterone derivatives for only 30% of the women. It is, therefore, possible that the effect of European HT regimens is different from what has been observed in American studies. In a French cohort study HT users mostly received a combination of a transdermal estradiol plus either progesterone or progesterone-derived progestins other than MPA and these women did not have an increased risk of breast cancer [39]. Although no large variations were seen between the effects of specific estrogens or specific progestagens in relation to breast cancer in the Million Women Study [12], a recent study by Fournier et al. [40] showed that breast cancer risk differed according to the type of progestogen that was used.

Among women without a surgical menopause, the multivariate logistic regression analysis revealed that age, alcohol use, smoking, parity, oral contraceptive use and family history of breast cancer were the most important indicators of HT use. Although not all studies, which have investigated potential indicators of HT use, have examined the same characteristics in multivariate analysis, many of them also found a relation between these characteristics and HT use in univariate analysis. Comparable results were found in a variety

of European countries such as Germany [10], Italy [23,41], Sweden [42], Norway [43] and the United Kingdom [24], as well as the United States [44–46]. In these studies HT was usually defined as taking estrogens alone or in combination with progestogens for the relief of climacteric problems, whereas in our study oral contraceptives used for menopausal complaints were also included in the HT group, which may have influenced our results. However, when we investigated the potential indicators for ET, combined HT and oral contraceptives for menopausal complaints separately, no relevant differences were observed.

Many studies have suggested that HT users have healthier lifestyles than women who do not use HT [10,44,42], which may have biased observational studies on HT and cardiovascular risk and, therefore, partly explain the discrepancy between findings from observational studies and randomized controlled trials. Our results do not show a generally healthier lifestyle among HT users as compared to non HT users. However, most of the important indicators in our study can be explained by endogenous hormone levels. The association between age and HT use may be due to the fact that in most women between 49 and 54 years old, menopause occurs and estrogen levels drop, which very often results in menopausal complaints and subsequently in the prescription of HT. For women over 55 years of age most menopausal problems are over and they are less likely to use HT. Previous use of oral contraceptives can be interpreted as willingness to use hormones and family history of breast cancer may worry women to get breast cancer themselves. Smoking has been associated with an earlier age at menopause [47], which is assumed to be due to lower endogenous estrogen levels [48]. If this is true, smokers will be more likely to use HT, which is in agreement with our finding. The level of endogenous estrogen, however, can probably not explain the relation between alcohol use and HT use. Women who drink alcohol appear to have higher endogenous estrogen levels [49–51] and, therefore, less HT use would be expected. In our study, however, alcohol drinkers were more likely to be current HT users. Finally, no consistent relation has been found in literature between number of children and endogenous hormone levels [52], which indicates that endogenous estrogen levels are unlikely to explain the relation between number of children and HT use. In this respect, the attitude

of women towards menopause and treatment might be relevant, which has been described in other studies [53,54].

The indicators of current HT use were somewhat different for women with a surgical menopause compared to women without a surgical menopause. The use of HT in women with a surgical menopause is probably mainly due to whether their ovaries are removed and some other indicators, such as lifestyle and reproductive factors are, therefore, less clearly observed.

Since this is a cross-sectional study and the data of characteristics were not available before women started HT use, the direction of some of the associations may be uncertain. However, characteristics such as parity were most probably present before the use of HT and are, therefore, not likely to be influenced by HT use. Nevertheless, the causality of the association cannot be determined due to the cross-sectional analysis and, therefore, we have chosen to use the word indicator for those characteristics that are associated with HT use.

A limitation of the present study is that data were collected between 1993 and 1997. Since then many reports have been published on the side effects of HT and the use of HT has been discussed heavily. It is possible that the frequency, duration and indicators of HT use in the Netherlands have changed in the recent past years. Therefore, constant guidance of prevalence rates of HT use is invaluable.

In conclusion, the frequency of HT use in the Netherlands is low compared to other western countries, but the prescription rates seem to be increasing over the years and the duration of use is rather long. HT use seems to be largely determined by factors that are known to affect endogenous estrogen levels, rather than by health awareness or life style.

Acknowledgement

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