




# Use of exogenous hormones and the risk of breast cancer: results from self-reported survey data with validity assessment

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## Abstract

**Purpose** Main aim was to estimate the association between use of exogenous hormones and breast cancer (BC) risk in a large population-based survey, and to assess the representativeness and overall validity of the data.

**Methods** The survey ‘Women’s Health and Use of Hormones’ was conducted in Finland in 2009, including 7,000 BC cases and 20,000 matched population controls. Conditional logistic regression was used to estimate odds ratios and their 95 % confidence interval. For validation, exposure prevalences were compared with population data from Statistics Finland and two large population-based surveys. **Results** We found positive associations with BC risk and exclusive use of hormone-releasing intrauterine device (HR IUD) in postmenopausal women (1.48, 95 % CI 1.10–1.99), when compared to never-users of any hormonal contraceptive and considering only prediagnostic use in cases. Regarding use of other hormonal contraceptives (HC), a positive association between long HC use ( $\geq 2$  years) and BC was observed in both groups, OR being

1.37 (95 % CI 1.12–1.68) for premenopausal and 1.11 (95 % CI 1.03–1.20) for postmenopausal women, when compared to never-users of other HC.

**Conclusions** Observed association between HR IUD use and risk of BC in postmenopausal women is worrying and deserves further attention. Selection bias seemed not to explain this result. Considering the increasing popularity of HR IUD use in, e.g., USA, impact of possible adverse effects in public health could be significant.

**Keywords** Hormonal contraceptives · Intrauterine device · Case–control study · Breast cancer · Epidemiology

## Introduction

Breast cancer (BC) is the most common cancer among Finnish women with approximately 4,500 new cases annually [1] and an age-standardized incidence rate of c. 90/100,000. Incidence has increased steadily over the past decade with approximately 1.3 % per year. This trend is expected to continue, and the age-standardized rate is predicted to reach 100/100,000 in year 2016 [2]. Currently, the incidence of BC increases markedly after 45 years of age and peaks at 60 years [2]. Nationwide organized screening started in Finland in 1987 and women aged 50–69 years are invited to mammography biennially [3].

Age and female gender are well-established risk factors for BC, together with family history with an approximately twofold increase in risk if one first-degree relative has been diagnosed with BC [4]. Previous history of BC and certain benign breast diseases increase the risk [5], as well as high breast density [6]. There is increasing evidence on the relationship between female sex hormones and BC [7]. Many full-term pregnancies and young age at first delivery

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decrease BC risk, whereas early age at menarche and old age at menopause increase it [8–10]. Other well-established risk factors include use of alcohol and postmenopausal weight gain which increase the risk, while breast feeding and physical exercise decrease it [11].

Studies on the association between use of hormonal contraceptives (HC) and risk of BC have reported conflicting results. The prospective Nurses' Health Study II concluded with a positive association between oral contraceptive use and the risk of BC [12], as did a case–control study in 2008 [13]. On the other hand, no increase in BC risk was found in a population-based case–control study [14]. The role of hormone-releasing intrauterine device (HR IUD) in the etiology of BC has also been under discussion, and the results are somewhat contradicting [15–18]. With respect to use of hormone replacement therapy (HRT), several studies have indicated that HRT use increases the risk of BC. The risk is even higher with longer duration of use and most specifically with the use of estrogen–progesterin combination [19–22].

A retrospective case–control study design is most useful in assessing lifestyle-related risk factors in rare diseases, where a prospective setup would be overly expensive and time-consuming. It is also convenient in obtaining information on exposures that cannot be measured by other means, e.g., with registry linkage. However, the retrospective nature of data collection creates potential for different biases to occur [23]. Validity of survey data and the role of non-response bias have long been of concern in epidemiologic research [24–26].

In this study, we aim to estimate the association between the use of exogenous hormones and BC risk and to assess the validity and representativeness of the Women's Health and Use of Hormones (WHH) survey with respect to various background and lifestyle factors. The direction and magnitude of selection and non-response bias will be studied, and additionally, we evaluate recall bias and exposure misclassification.

## Materials and methods

The nationwide WHH survey was conducted in Finland in 2009. Cases were defined by identifying all women diagnosed with BC (in situ or invasive) at 22–60 years of age between January 01, 2000, and December 31, 2007. Case identification was done from the Finnish Cancer Registry, which is population based and nationwide and covers about 99 % of solid tumors [27]. In all, 14,815 women were identified, of whom 1,550 had died before the survey, leaving 13,265 breast cancer cases in the data (Fig. 1).

Controls were retrieved from the central population register by a third party under a delivery agreement. First,

four (4) controls per one case were matched with age at diagnosis ( $n = 47,511$ ). Erroneous age-matching led to an imbalance in the number of cases and controls, and to correct for this, a second matching was conducted by birth year ( $n = 16,842$ ). Total number of controls was thus 64,353.

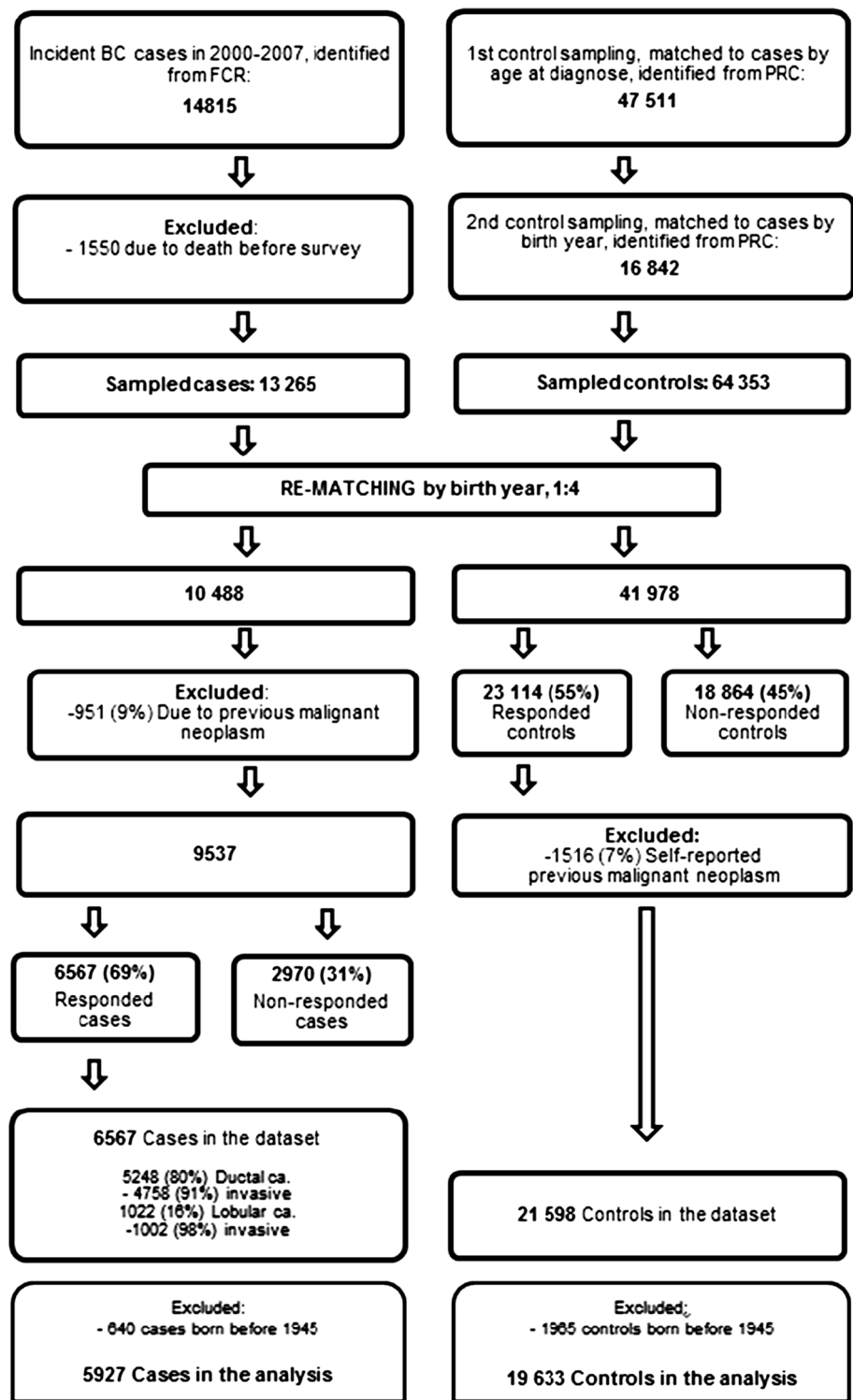
To remove any remaining imbalance in the number of cases and controls, a further rematching by birth year was conducted to reach an exact ratio of 1:4. Hence, cases and controls were randomly excluded, and 10,448 women with BC and 41,978 controls were left in the data. Of the cases, 951 had had some previous malignancy (data from Cancer Registry) and were therefore excluded; leaving 9,537 breast cancer cases for the survey, out of whom 6,567 responded (69 %). Of the controls, 23,114 responded the survey (55 %), and 1,516 reported a previous malignancy (self-report) and were thus excluded, leaving 21,598 controls in the analytical data set. The study subjects were born between 1939 and 1984. For better comparability with the other surveys, WHH responders born before 1945 (640 cases, 1965 controls) were left out from this study to have equal age cohorts in all the surveys.

The WHH survey was initially developed to address the association between the use of hormones and risk of BC [17]. Additionally, the survey mapped out several possible risk factors for BC, such as family history of BC, age at menarche, smoking, alcohol use, and body mass index (BMI). The survey was self-administered and identical for cases and controls. The aims and objectives of the study were explained at the cover letter of the survey. The filled and returned survey was considered as an informed written consent.

The primary exposures of interest were use of HC, IUD, and HRT. Original categorization for HC use duration was 'None,' '<1 month,' '1–6 months,' '>6 months–<2 years,' '2–4 years,' '>4–8 years,' '>8–12 years,' '>12–16 years,' '>16–20 years,' '>20–25 years,' and '>25 years.'

For analysis, these were pooled to form a binomial variable, categories '<1 month,' '1–6 months,' and '>6 months to < 2 years' being categorized into the use of less than 2 years, the latter ones counting as usage of 2 years or more. Use of IUD was asked as ever- versus never-use of an intrauterine device, and for ever-users, also the type of the device was asked, the alternatives being copper IUD, hormone-releasing IUD, and other IUD. For further analysis, also a referent category with never-users of any hormonal contraceptive (HR IUD or other hormonal contraceptive) was formed. Use of HRT was questioned as ever- versus never-use without duration specification. Information on the current use of HRT is used only as a reference factor in the survey validation (Supplement T1). It was asked binomially as currently using or not using HRT without further specifications.

**Fig. 1** Flowchart of the number of study subjects from identification to the statistical analysis in WHH (Women’s Health and Use of Hormones)



Conditional logistic regression was used to estimate odds ratios (ORs) and 95 % confidence interval (CI). Analyses were stratified by age: those aged 50 years or less at survey, representing premenopausal women, and those aged 51 or over, representing postmenopausal respondents. Univariate results were adjusted for birth year, multivariate

analysis included HC use, use of HR IUD and HRT, age at menarche, parity, family history of BC, BMI, education, smoking, and alcohol use.

To assess validity, we compared exposure prevalences from the WHH with national data from Official Statistics Finland (OSF) and two other nationwide surveys: the

Health Behavior and Health among the Finnish Adult Population in 2010 (AVTK, 1,583 female responders) and the national FINRISK study from 2007 (3,346 female responders) [28, 29]. Data from OSF were available regarding education, parity, and marital status. Additionally, the AVTK and FINRISK studies provided information on alcohol use, smoking, and BMI and on the use of HC, HR IUD, and HRT.

The study was approved by the ethical committee of HUS (Helsinki and Uusimaa Health District), decision number 322/E0/07, and permission for data linkage was obtained from the National Institute of Health and Welfare (THL, former STAKES), decision number 2920/605/2008.

## Results

The overall response rate in the WHH was 69 % among the cases and 55 % among the controls (Supplement T1). Median age of both cases and controls was 57.5 years. Response percentages varied from 52 to 69 % between the age groups, being lowest among controls aged 35–44 years (52 %) and highest in cases aged 35–44 and 55–64 years (69 %).

A statistically significant increase in BC risk was observed for postmenopausal women with respect to exclusive use of HR IUD, when comparing ever-users to those using or having exclusively used a copper intrauterine device and after adjusting for other risk factors (OR 1.52, 95 % CI 1.14–2.02). When comparing exclusive use of HR IUD to never-users of any hormonal contraceptive and when including only cases reporting IUD use before BC diagnosis, an odds ratio of 1.48 (95 % CI 1.10–1.99) was observed in postmenopausal women.

Ever-use of HC (other than intrauterine device) was associated with increased BC risk among premenopausal respondents (OR 1.32, 95 % CI 1.08–1.61, Table 1), when compared to never-users. A slight increase was also noted in postmenopausal women (OR 1.08, 95 % CI 1.01–1.16). To evaluate the role of more current HC use, we also did the analysis restricting on cases diagnosed in 2004–2007, then observing an OR 1.14, 95 % CI 1.02–1.29, in contrast to that of 0.91, 95 % CI 0.80–1.03 when including only those diagnosed in the first 2 years (2000–2001) of the recruitment period (results not shown). Regarding duration of use, a positive association between long HC use ( $\geq 2$  years) and BC was observed in both age groups, OR being 1.37 (95 % CI 1.12–1.68) for premenopausal and 1.11 (95 % CI 1.03–1.20) for postmenopausal women, when compared to never-users of HC. Unexpectedly, ever-use of HRT was inversely associated with the risk of BC among postmenopausal women when compared to never-users (OR 0.72, 95 % CI 0.67–0.78).

Increased odds ratios were expectedly obtained for those with high education (OR 1.18, 95 % CI 1.07–1.31 for postmenopausal women), when compared to those with  $\leq 9$  years of education (Table 1). Having a family history of BC was associated with increased risk in both age groups, OR 1.85 (95 % CI 1.54–2.22) for premenopausal and OR 1.66 (95 % CI 1.52–1.81) for postmenopausal women. Risk of BC was elevated also with early age at menarche ( $\leq 12$  vs.  $\geq 13$  years) in both age groups, OR 1.26 (95 % CI 1.10–1.45) in premenopausal and OR 1.11 (95 % CI 1.03–1.20) in postmenopausal women. Parity was inversely associated with BC risk regardless of the respondent's age, OR 0.69 (95 % CI 0.56–0.86) in premenopausal women and OR 0.83 (95 % CI 0.74–0.94) for postmenopausal respondents. Regarding BMI, a statistically significant inverse association was noted for BMI  $\geq 30$  kg/m<sup>2</sup> among postmenopausal women, OR 0.83 (95 % CI 0.75–0.91). No relationship was observed between smoking or alcohol use and BC risk in either of the age groups when comparing ever-users to never-users.

## Validity assessment

Comparisons of the background variables between WHH and OSF are presented in Table 2. The average difference between self-reported academic education of the controls in the WHH and OSF [30] was 8 % points (pp), being largest among the 25- to 34-year-olds. There were 18 pp more academically educated responders among WHH cases and 16 pp more among the controls in this age group, compared to respective population prevalence. In older age groups, the difference varied between 6 and 8 pp among the cases and from 4 to 6 pp among the controls.

Regarding percentages of women ever given birth or been pregnant, the figures of the controls in WHH differed on average by 9 pp from the OSF percentages. The largest difference was again seen in the youngest age group (25–34 years), where 68 % of the cases and 67 % of the controls in WHH reported being parous, the corresponding percentage being 49 % in OSF. Parity figures were more concordant in other age groups.

According to OSF, the proportion of married women in the population of the target age cohort in 2009 was 37 %, which is over twofold less than the figure obtained from the WHH. In the WHH, however, marriages and common-law marriages were combined in one category; in the OSF, they are reported separately. The percentages of divorced women were by definition more comparable. While the average percentage of women reporting to be divorced or separated was 12 % in the WHH, the official figure drawn from the OSF was 11 %.

Comparisons of the different surveys, WHH, AVTK, and FINRISK, are presented in Supplement T1. Overall,

**Table 1** Number of subjects and odds ratios for risk factors of breast cancer in Women's Health and Use of Hormones survey

Variable	Category	Age at survey							
		25–50				51–64			
		Ca	Co	OR (CI 95 %) univariate	OR (CI 95 %) multivariate <sup>a</sup>	Ca	Co	OR (CI 95 %) univariate	OR (CI 95 %) multivariate <sup>a</sup>
HC use <sup>b</sup>	Never	120	507	1.0	1.0	1,304	4,450	1.0	1.0
	Ever	994	3,208	<b>1.27 (1.05–1.54)</b>	<b>1.32 (1.08–1.61)</b>	3,459	11,290	1.04 (0.98–1.11)	<b>1.08 (1.01–1.16)</b>
	NA	3	11			47	165		
HC use duration	<2 year	126	487	1.07 (0.82–1.38)	1.12 (0.85–1.46)	882	3,229	0.95 (0.87–1.04)	0.99 (0.90–1.09)
	≥2 year	883	2,709	<b>1.33 (1.10–1.62)</b>	<b>1.37 (1.12–1.68)</b>	2,673	8,382	<b>1.08 (1.01–1.16)</b>	<b>1.11 (1.03–1.20)</b>
	Never	120	507	1.0	1.0	1,304	4,450	1.0	1.0
Use of IUD	NA	108	530			1,255	4,294		
	HR IUD exclusively	75	261	<b>0.60 (0.44–0.82)</b>	<b>0.59 (0.42–0.82)</b>	73	137	<b>1.50 (1.14–1.96)</b>	<b>1.52 (1.14–2.02)</b>
	CU IUD exclusively	90	173	1.0	1.0	269	793	1.0	1.0
	NA	952	3,292			4,468	14,975		
	HR IUD exclusively	75	261	0.94 (0.73–1.21)	1.00 (0.77–1.30)	73	137	<b>1.57 (1.24–2.00)</b>	<b>1.63 (1.26–2.11)</b>
	CU IUD exclusively	90	173	<b>1.57 (1.24–1.98)</b>	<b>1.71 (1.34–2.20)</b>	269	793	1.08 (0.94–1.23)	1.14 (0.99–1.32)
	Never-use of IUD	309	998	1.0	1.0	686	2,138	1.0	1.0
	NA	643	2,294			3,782	12,837		
	HR IUD exclusively <sup>c</sup>	50	261	0.77 (0.54–1.10)	0.79 (0.54–1.17)	56	137	<b>1.36 (1.03–1.79)</b>	<b>1.48 (1.10–1.99)</b>
	CU IUD exclusively <sup>c</sup>	48	173	1.07 (0.75–1.54)	1.21 (0.83–1.78)	175	793	<b>0.78 (0.66–0.93)</b>	0.86 (0.72–1.04)
HRT use	Never-use of any HC	50	190	1.0	1.0	370	1,258	1.0	1.0
	NA	593	2,104			3,412	11,579		
	Never	1,050	3,459	1.0	1.0	2,822	8,398	1.0	1.0
Education	Ever	39	194	<b>0.69 (0.50–0.95)</b>	0.73 (0.51–1.05)	1,833	7,103	<b>0.78 (0.73–0.82)</b>	<b>0.72 (0.67–0.78)</b>
	NA	28	73			155	404		
	≤9 years	379	1,248	1.0	1.0	2,645	9,236	1.0	1.0
	10–12 years	185	581	1.04 (0.87–1.24)	1.01 (0.82–1.24)	409	1,268	<b>1.12 (1.01–1.24)</b>	1.12 (0.99–1.27)
	13–16 years	332	1,209	0.91 (0.78–1.05)	0.91 (0.76–1.08)	1,029	3,303	<b>1.08 (1.01–1.16)</b>	<b>1.09 (1.00–1.19)</b>
Family history	≥17 years	217	659	1.07 (0.90–1.26)	0.98 (0.80–1.20)	701	1,973	<b>1.21 (1.11–1.32)</b>	<b>1.18 (1.07–1.31)</b>
	NA	4	29			26	125		
	No	933	3,394	1.0	1.0	3,856	13,903	1.0	1.0
Menarche	Yes	176	297	<b>1.91 (1.63–2.25)</b>	<b>1.85 (1.54–2.22)</b>	878	1,726	<b>1.67 (1.55–1.80)</b>	<b>1.66 (1.52–1.81)</b>
	NA	8	35			76	276		
	≤12 years	446	1,287	<b>1.22 (1.08–1.37)</b>	<b>1.26 (1.10–1.45)</b>	1,457	4,452	<b>1.11 (1.04–1.18)</b>	<b>1.11 (1.03–1.20)</b>
Parity	≥13 years	669	2,423	1.0	1.0	3,325	11,382	1.0	1.0
	NA	2	16			28	71		
	No	194	510	1.0	1.0	585	1,533	1.0	1.0
Parity	Yes	919	3,205	<b>0.78 (0.67–0.91)</b>	<b>0.69 (0.56–0.86)</b>	4,197	14,284	<b>0.80 (0.73–0.87)</b>	<b>0.83 (0.74–0.94)</b>
	NA	4	11			28	88		

**Table 1** continued

Variable	Category	Age at survey							
		25–50				51–64			
		Ca	Co	OR (CI 95 %) univariate	OR (CI 95 %) multivariate <sup>a</sup>	Ca	Co	OR (CI 95 %) univariate	OR (CI 95 %) multivariate <sup>a</sup>
BMI (kg/ m <sup>2</sup> ) <sup>d</sup>	<25	565	1,917	1.0	1.0	1,989	6,376	1.0	1.0
	25–29.9	354	1,081	1.10 (0.96–1.25)	1.01 (0.87–1.17)	1,671	5,274	1.01 (0.95–1.08)	0.97 (0.90–1.05)
	≥30	157	578	0.94 (0.78–1.12)	0.86 (0.70–1.06)	815	3,007	<b>0.88 (0.81–0.96)</b>	<b>0.83 (0.75–0.91)</b>
	NA	41	150			335	1,248		
Smoking	Never	612	2,011	1.0	1.0	2,589	8,437	1.0	1.0
	Ever	501	1,698	0.98 (0.87–1.1)	0.95 (0.82–1.09)	2,158	7,287	0.97 (0.92–1.03)	0.99 (0.92–1.06)
	NA	4	17			63	181		
Alcohol use	No/Occ.	603	1,927	1.0	1.0	2,714	8,989	1.0	1.0
	Regul.	510	1,779	0.93 (0.82–1.04)	0.89 (0.78–1.02)	2,049	6,768	1.01 (0.95–1.07)	0.99 (0.93–1.07)
	NA	4	20			47	148		

Effect estimates with statistical significance are in bold

<sup>a</sup> Multivariate model including all listed variables, except for HC use duration, being restricted to ever-users of HC only. In analyses of HC and HR IUD use, the other contraceptive method was excluded from the model. ORs regarding confounding variables were derived from the model including HC use only

<sup>b</sup> Including ever- versus never-use of hormonal contraceptives such as oral contraceptive pills, contraceptive patches, contraceptive implant, and contraceptive injection

<sup>c</sup> Only including cases reporting IUD use before breast cancer diagnosis

<sup>d</sup> Calculated from the height and weight reported in the questionnaire with the formula weight/(height<sup>2</sup>)

the largest differences were observed with regard to HRT use and regarding parity, education, and HR IUD use in the youngest age group. Compared to current HRT users in AVTK and FINRISK, there were significantly more ever-users of HRT among the controls in the WHH, and a difference of 5 pp was noted in age group of 45–54 years and 19 pp among the 55- to 64-year-olds. With respect to parity, young controls (25–34 years) in the WHH reported significantly more often to be parous, the difference to FINRISK being 24 pp. Differences in the older age groups were much smaller, 3–5 pp. Also regarding education, the difference was highest in the youngest age group, 10 pp. Other age groups only differed by 0–2 pp. There were 11 pp more ever-users of HR IUD among WHH controls in the youngest age group compared to FINRISK respondents.

## Discussion

We detected positive associations between BC risk and use of HC and HR IUD. Inverse associations were observed regarding ever-use of HRT. With respect to use of HR IUD, a positive association with the risk of BC was observed among postmenopausal women. This finding is concordant with those of Lyytinen et al. and Soini et al., who reported an increased BC risk of postmenopausal users of HR IUD from

register-based studies [16, 37, 42]. This may be due to some estrogen-related mechanisms promoting tumor growth, or it may be a result of selection bias, when use of HR IUD is more often a preferred method of contraception or used as part of hormone replacement therapy among women with inherently increased risk of BC, e.g., due to family history. The reason for the observed association only in postmenopausal women is also unclear, and most logical explanation would be latent phase between the exposure and the onset of BC. In this study, we had the possibility to adjust the analysis for other major risk factors for BC, including family history of breast cancer. The results imply that confounders do not have an effect on the estimated association between HR IUD use and risk of BC. In comparison, the earlier study with partly the same WHH data reported a rather similar adjusted odds ratio for women ≤50 years of age as in our study [17]. Women 50 years or older were not included in the earlier analyses.

Regarding other HC use, the results are mainly in line with previous research, with an elevated BC risk especially among the young women. A large prospective study of women aged 24–43 years concluded that current HC use carries an excess risk of BC [12]. Correspondingly, a case-control study by Rosenberg et al. [13] suggested a positive association between current HC use and risk of BC, more specifically in cases diagnosed in the recent years. A

**Table 2** Percentages of women by age at survey regarding selected risk factors for breast cancer in WHH (Women's Health and Use of Hormones) and Official Statistics of Finland (OSF)

Variable	25–34					35–44				
	OSF	WHH cases, % (n)	WHH controls, % (n)	$\Delta$ cases	$\Delta$ controls	OSF	WHH cases, % (n)	WHH controls, % (n)	$\Delta$ cases	$\Delta$ controls
Education, academic degree %	15 <sup>c</sup>	33 (11)	31 (39)	<b>+18</b>	<b>+16</b>	15 <sup>c</sup>	22 (83)	20 (243)	<b>+7</b>	<b>+5</b>
Marital status, divorced %	5 <sup>b</sup>	9 (3)	5 (6)	<b>+4</b>	<b>0</b>	13 <sup>b</sup>	10 (40)	7 (86)	<b>-3</b>	<b>-6</b>
Parity, yes %	49 <sup>d</sup>	68 (86) <sup>a</sup>	67 (86) <sup>a</sup>	<b>+19</b>	<b>+18</b>	78 <sup>d</sup>	81 (307) <sup>a</sup>	84 (1,025) <sup>a</sup>	<b>+3</b>	<b>+6</b>
Variable	45–54					55–64				
	OSF	WHH cases, % (n)	WHH controls, % (n)	$\Delta$ cases	$\Delta$ controls	OSF	WHH cases, % (n)	WHH controls, % (n)	$\Delta$ cases	$\Delta$ controls
Education, academic degree %	10 <sup>c</sup>	16 (301)	14 (891)	<b>+6</b>	<b>+4</b>	6 <sup>c</sup>	14 (523)	12 (1,459)	<b>+8</b>	<b>+6</b>
Marital status, divorced %	20 <sup>b</sup>	15 (281)	15 (910)	<b>-5</b>	<b>-5</b>	21 <sup>b</sup>	15 (542)	16 (1,881)	<b>-6</b>	<b>-5</b>
Parity, yes %	83 <sup>d</sup>	86 (1,588) <sup>a</sup>	89 (5,542) <sup>a</sup>	<b>+3</b>	<b>+6</b>	85 <sup>d</sup>	88 (3,198) <sup>a</sup>	90 (10,836) <sup>a</sup>	<b>+3</b>	<b>+5</b>

Effect estimates with statistical significance are in bold

$\Delta$  Difference between the cases and controls in WHH and OSF in percentage points

<sup>a</sup> Have been pregnant

<sup>b</sup> OSF: Population structure [e-publication]. ISSN = 1797-5395. Helsinki: Statistics Finland [referred: 22.10.2014]. Access method: [http://tilastokeskus.fi/til/vaerak/index\\_en.html](http://tilastokeskus.fi/til/vaerak/index_en.html)

<sup>c</sup> OSF: Educational structure of population [e-publication]. ISSN = 2242-2919. Helsinki: Statistics Finland [referred: 22.10.2014]. Access method: [http://tilastokeskus.fi/til/vkour/index\\_en.html](http://tilastokeskus.fi/til/vkour/index_en.html)

<sup>d</sup> OSF: Population structure [e-publication]. ISSN = 1797-5395. Annual Review 2009, Women by age, number of children, and the proportion of those having given birth December 31, 2009. Helsinki: Statistics Finland [referred: 22 October 2014]. Access method: [http://www.tilastokeskus.fi/til/vaerak/2009/01/vaerak\\_2009\\_01\\_2010-09-30\\_tau\\_005\\_en.html](http://www.tilastokeskus.fi/til/vaerak/2009/01/vaerak_2009_01_2010-09-30_tau_005_en.html)

review by Gierisch and colleagues also concluded with an increased BC risk of recent use of HC, as did Beaver et al. [38, 39]. Increased risk estimates for recent HC users logically relate to younger women, who still are or have recently been in need for contraception. This intriguing observation was also done from the WHH, and it deserves further attention in future studies, considering that there are also studies reporting null associations between HC use and BC risk [40, 43].

Our results also implied an inverse association between HRT use and risk of BC among postmenopausal women, which is completely opposite to previous research [15, 16]. Stratifying the analysis by family history status did not change the estimates (results not shown). Controls in the older age group using or having used HRT are clearly overrepresented in the WHH, which is probably the reason for this surprising finding. It seems evident that the estimate for association between HRT use and BC risk is biased and should be considered with caution.

Regarding traditional BC risk factors, statistically significant associations were observed with respect to high

education, family history of BC, early age at menarche, and nulliparity, suggesting validity of the survey. The reported multivariate ORs regarding confounding variables were derived from the model including HC use only, but the estimates varied very little between the different models.

The observed increased BC risk in women with high education is in line with previous results, e.g., that of Braaten et al. [41]. Regarding family history of BC, increased risk estimates from the WHH study reflect those obtained in large prospective studies [31]. In WHH, the association was slightly stronger in premenopausal women, which is concordant with previous findings [4]. Association between early age at menarche and BC risk was also in line with results from the referent studies, all reporting slightly elevated risk effects with earlier menarche age [31, 33–36]. Also age-adjusted odds ratios for parity in relation to BC risk were of the same magnitude in WHH as those reported by Reeves et al. [33] and Kotsopoulos and colleagues [36], all concluding with some 20–25 % lower BC risk estimates for parous women.

An inverse association between obesity ( $\geq 30$  kg/m<sup>2</sup>) and risk of BC was observed in postmenopausal women.

This is contradictory to previous findings. Kotsopoulos et al. reported a 50–60 % increase in BC risk in women with BMI  $\geq 30$  kg/m<sup>2</sup>. It is fairly commonly accepted that a positive association between obesity and BC risk concerns mainly postmenopausal women and the effect might be the opposite in premenopausal women. In WHH, the problem is most likely in the retrospective nature of the survey, where cases might have lost weight after cancer diagnosis. It is also possible that selection bias has resulted in well-educated women with healthy lifestyle and lower BMIs in responding health-related surveys more eagerly.

We did not find association between smoking or alcohol use and the risk of BC. Also meta-analyses by Hamajima and colleagues [32] as well as that by Nelson et al. [31] both reported nonsignificant risk estimates for ever versus never smokers. Regarding alcohol use, whereas Nelson et al. reported no association in their meta-analysis, results from the Million Women Study suggested a significant association between moderate alcohol consumption and BC risk [33].

### Considering validity

In the WHH, response activity of the controls was substantially lower compared to that of the cases. There was variation between the age groups; the difference in compliance between cases and controls was largest, on average 15 pp, in the oldest age groups. In general, the response rates were highest among the older responders in all considered surveys.

OSF was considered to offer nearly complete data on the given variables, and hence, it enabled us to reliably assess the level of non-response bias in the WHH survey [44]. AVTK and FINRISK studies were considered suitable referents due to their established nature as routine, official nationwide health surveys conforming to the guidelines of the European Health Risk Monitoring project [45].

Exposures that are evidently related to an increased BC risk, such as high education and nulliparity, were seen in WHH as large percentages of academically educated, nulliparous cancer cases, compared to that of the controls. Comparison of the WHH and OSF also showed great disparities in the percentages of academically educated, parous women. This phenomenon was especially seen among young study participants, the differences evening out in the older age groups. This returns to the well-known phenomenon, where survey responders often are highly educated and living in a relationship [46]. This makes factors confounded by the socioeconomic status more difficult to assess and may reduce the representativeness of the results. It also affects, e.g., smoking and alcohol use and estimations of their role in the etiology of BC. To account for the differences in the distribution of the educational level in the WHH responders versus non-responders, we stratified

the analysis of HR IUD and HC use by education. This did not change the results regarding the association between HR IUD and BC, the odds ratio still being stronger and statistically significant in postmenopausal women regardless of education. With respect to HC use, the observed effect in premenopausal women was diluted and statistically significant association was no longer seen in either age group (results not shown).

As with all retrospective case–control studies, recall bias was of concern in this study. Time between cancer diagnosis and the survey varied from 1 to 9.5 years, the median being 5.5 years. Generally, the longer the time from the diagnosis, the fewer respondents. Likewise, the longer the time elapsed between diagnosis and the survey, the more may be missed of aggressive types of cancer due to death. This was observed in the WHH study, where some 70 % of the cancer cases who died before the survey were metastatic at diagnosis, whereas less than 40 % of the cancers included in the study were metastatic at diagnosis. There were no differences in spreading of the cancer among the responders and non-responders.

Differences between the surveys indicate that non-response bias is more likely in a topic-specific survey such as the WHH and especially when the study participants are aware of the main study question. This observation is concordant with earlier estimations reporting that people are 40 % more likely to respond to a survey with a topic of special interest to them [47]. It is possible that knowing the focus of the WHH survey (hormone use) may have drawn more hormone-users to answer the survey. Also, use of hormonal contraceptives may not have been considered as ‘use of hormones’ in the same sense as HRT use, resulting in more representative user prevalences regarding contraceptives. It must also be noticed that in the WHH, the percentages of HRT users include also women using HRT due to hysterectomy and/or oophorectomy. Nevertheless, discrepancies in HRT user prevalence between the surveys are considerable. In contrast, reporting of some lifestyle factors was surprisingly consistent between the surveys, concerning for instance smoking. Overall, the WHH survey seemed to serve well with respect to use of hormonal contraceptives as well as regarding most of the background variables and potential confounders included in the questionnaire. The above-mentioned biases must, however, be taken into account when interpreting the results from surveys.

In conclusion, the observed association between HR IUD use and risk of BC in postmenopausal women deserves further attention, since the estimate is not likely to be severely biased. Even if the potential increase in risk of BC produced by HR IUD use would be small, taken the high prevalence of their use into account, the impact in public health could be considerable. Previous studies on the topic are scarce and an extensive prospective cohort study



is encouraged. Correspondingly, the increased BC risk estimates observed especially in premenopausal women regarding other HC use and elevated risk estimates for women with recent diagnosis are also of interest. The surprising HRT finding is very likely to be biased due to lack of representativeness of the HRT user population and should be ignored.

We emphasize the benefits of the use of reference population information on risk factors whenever available in order to assess potential bias, especially in case–control studies with survey information. This increases validity and improves interpretation of the results as well as guide in leaving out such study questions that are severely biased in the future studies.

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**Contribution statement** SH and JP made data analysis and wrote the manuscript. MK and EP designed the WHH study and related data collection. NM, TS, EP, and MK critically commented the manuscript.

#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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