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Miriam Heinig, Sarina Schwarz, Ulrike Haug

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Corresponding author

Ulrike Haug

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Title: Self-selection for mammography screening according to use of hormone replacement therapy: A systematic literature review

Authors and affiliations: Miriam Heinig^a, Sarina Schwarz^a, Ulrike Haug^{a, b}

a Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Achterstraße 30, 28359 Bremen, Germany

b Faculty of Human and Health Sciences, University of Bremen, Grazer Str. 2, 28359 Bremen, Germany

E-Mail: heinig@leibniz-bips.de (Miriam Heinig), sschwarz@leibniz-bips.de (Sarina Schwarz)

Corresponding author:

Prof. Dr. Ulrike Haug

Leibniz Institute for Prevention Research and Epidemiology – BIPS

Department of Clinical Epidemiology

Achterstraße 30, 28359 Bremen, Germany

Phone: +49-(0) 421-218-56862; Fax: +49-(0)421-218-56821

E-Mail: haug@leibniz-bips.de

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Abstract

Mammography screening participation may be influenced by the awareness of an increase in breast cancer risk due to hormone replacement therapy (HRT), which received particular attention upon publication of the Women's Health Initiative (WHI) trial results in 2002. Our aim was to synthesize evidence on a potential self-selection for mammography screening according to HRT use. We systematically searched the literature (MEDLINE, EMBASE, CINAHL) for studies reporting on the association between HRT use and mammography screening participation. Data were extracted independently by two reviewers.

Overall, 2018 studies were identified. Of these, 32 studies from nine countries, predominantly from North America (50%) and Europe (28%), were included. In studies from all countries and 94% of all studies, higher mammography screening uptake among HRT users compared to non-users was reported. In all 21 studies reporting an odds ratio, the association was positive, and in about 70% of these studies, this association was ≥ 2 . This also held true for studies exclusively using data collected before publication of the WHI findings in 2002 (63% of all studies). The association was not restricted to certain types of screening (organized vs. opportunistic) or certain types of HRT (combined vs. estrogen-only).

We found a consistent and relevant association between mammography screening uptake and HRT use. This is of considerable relevance for the design and interpretation of studies investigating risk factors or evaluating preventive measures for breast cancer.

Keywords: Hormone replacement therapy; breast cancer screening; mammography screening; self-selection; screening participation

Introduction

Combined estrogen-progesterone hormone replacement therapy (HRT) was classified as carcinogenic to humans by the World Health Organization (WHO) in 2007 [1] after observational studies and the Women's Health Initiative (WHI) trial had reported an up to twofold increased risk of breast cancer in users of combined HRT [2-4]. For estrogen-only HRT, no increase in breast cancer risk was reported in the second trial arm of the WHI [5], while some observational studies suggested a time-dependent risk [6, 7], and even a protective effect has been reported [8]. The findings of the WHI trial published in 2002 received considerable attention from the media [9, 10] and thus had a significant impact on the perception of the risks related to HRT in the medical community and the general public. In Europe, the prevalence of both combined and estrogen-only HRT has decreased in many countries and was estimated at 5–10% in 2010 [11]. Recent data on the prevalence of HRT use are sparse.

Among women who are still prescribed HRT, the awareness of the increased breast cancer risk associated with this medication may have an impact on the decision to attend breast cancer screening—possibly reinforced by their physicians' counseling [12]. This can lead to a larger proportion of HRT users among screening participants compared to non-participants. Knowledge on this potential self-selection is relevant in many regards. First, observational studies evaluating the effect of mammography screening on breast cancer mortality could be biased if self-selection according to HRT use played a role but was not considered in the analyses. Second, when investigating the effect of HRT use on breast cancer risk, higher screening participation among HRT users could lead to overestimation of breast cancer risk because of overdiagnosis. This means that breast cancers that would never have caused any symptoms or problems are overrepresented among HRT users. This would bias the association of HRT on breast cancer [13, 14].

However, evidence on a potential self-selection for mammography screening according to HRT use has not been synthesized so far. To fill this research gap, we aimed to

systematically review the literature for studies providing information on the association between HRT use and participation in mammography screening.

2. Material and methods

2.1. Search strategy

To summarize evidence regarding the association between HRT use and participation in mammography screening, we systematically searched the MEDLINE, EMBASE, and CINAHL databases for relevant studies published by September 2018. A detailed description of our search strategy is provided in Appendix A. In brief, for the MEDLINE search we used the Medical Subject Heading (MeSH) terms *mammography*, *mass screening*, *early detection of cancer*, and *hormone replacement therapy*, as well as related keywords. For the searches in EMBASE and CINAHL, we translated MeSH terms to equivalent Emtree and CINAHL subject headings. The search was complemented by cross-referencing. Authors of potentially relevant conference contributions were contacted and asked if a full publication was available. We only searched for articles published in German or English for reasons of language comprehension. No restrictions were placed on study design or type of mammography screening (organized vs. opportunistic). Studies focusing exclusively on breast cancer patients were excluded as they do not provide information on HRT use and screening participation in the general population. We only included studies reporting prevalences of HRT use among participants in mammography screening vs. non-participants or participation rates among HRT users vs. non-users or measures of associations regarding these two variables. The title and abstract of each retrieved study were screened for relevance. The full text was reviewed if the abstract indicated that the article provided information on the association between HRT use and participation in mammography screening.

2.2. Data extraction

For each study, we extracted the following information in a standardized manner: author, year of publication, country of origin, characteristics of the study population (sample size of HRT-related analyses, age), time period of data collection, type of mammography screening (organized, i.e., a program with an invitation system vs. opportunistic, i.e., screening offered without invitation), assessment of HRT use (method of data collection, categorization of the information), assessment of screening participation (method of data collection, definition of participation) as well as the outcomes of interest for this review, i.e., the association between HRT use and screening participation or the prevalence of these factors in the respective groups. Regarding the definition of screening participation, “on-schedule” refers to participation according to the recommended screening interval in the respective program. In terms of the results, we extracted—as far as available—the unadjusted results because we were mainly interested in the association between HRT and screening participation rather than in the factors that may explain this association (i.e. we did not strive for a causal interpretation). Only in studies including women <50 years, we extracted the age-adjusted rather than the unadjusted results (as far as available). The data were extracted from each eligible study by two authors (MH and SS) and any discrepancies were resolved by consensus. We sorted the studies by country of origin and—within countries—by the earliest year of data collection.

The systematic review was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [15]. The PRISMA checklist is provided in Appendix B.

3. Results

The initial search identified 2018 records after removal of duplicates (Figure 1). Of those, 51 studies were selected for full text review and 25 studies were included. Another seven relevant studies were identified by cross-referencing, yielding 32 studies in total for inclusion in this review [14, 16-46]. A list of studies excluded after full-text review with reasons for exclusion is available in Appendix C.

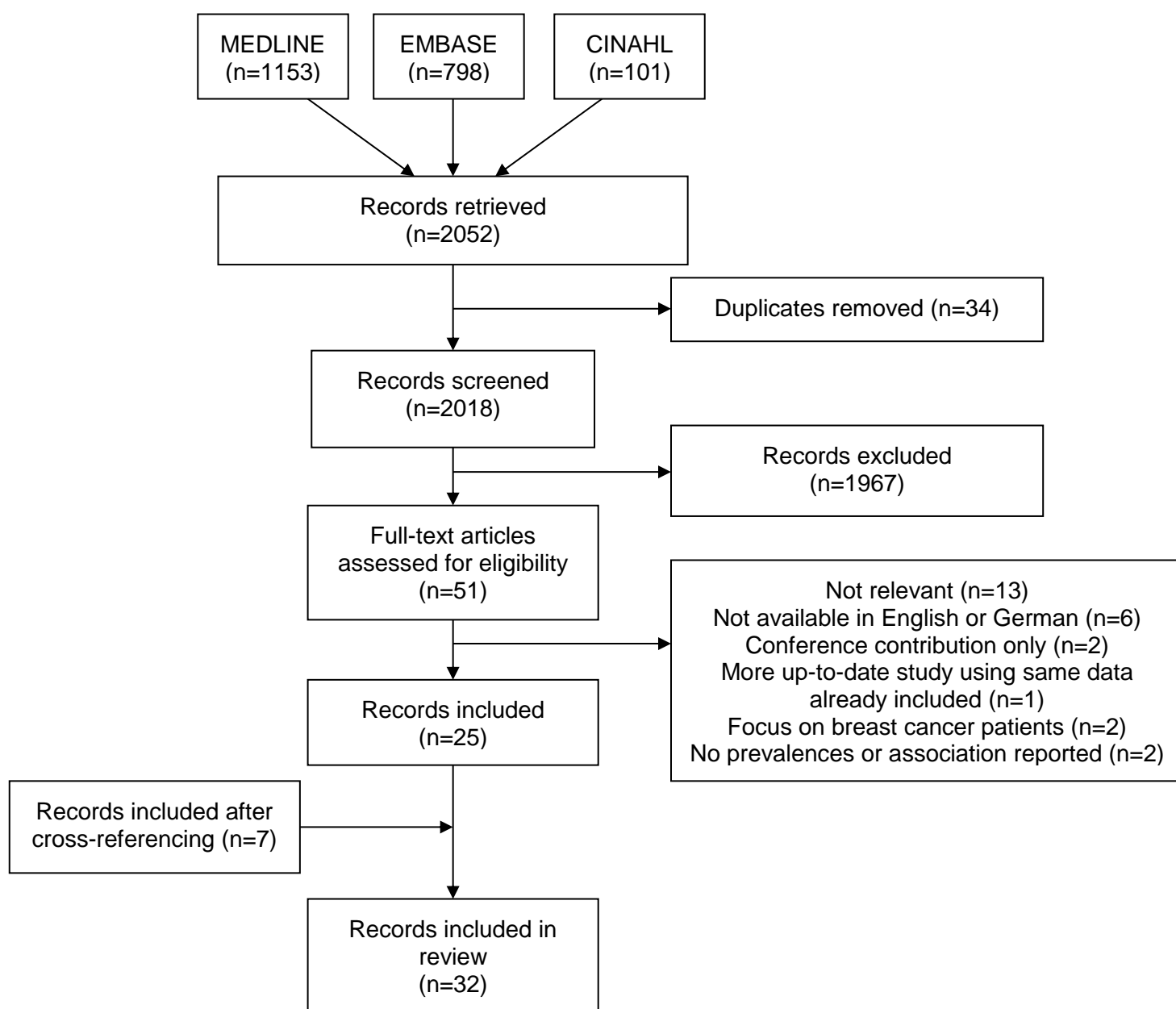


Figure 1 PRISMA flow diagram of study selection

Half of the included studies (16/32) were conducted in North America (USA: 14, Canada: 2) [14, 16-30], and about one quarter (9/32) in Europe (UK: 3, Spain: 2, France: 2, Sweden: 2) [31-39]. Of the remaining seven studies, three were conducted in Australia, three in Brazil, and one in Taiwan [40-46]. Sample sizes ranged from 149 to 1,371,218 women, and the age of the study population ranged from 32 to 101 years. Fourteen of the 32 studies (44%) did not exclusively include postmenopausal women or women aged 50 years or older but also younger women [17, 19-21, 24, 27, 28, 32, 36, 38, 42, 43, 45, 46]. Four of these fourteen studies did not provide age-adjusted results [21, 32, 43, 45]. 63% of the studies (20/32), data were collected before 2002 only, i.e., before publication of the WHI trial findings [14, 16-25, 29-34, 37, 38, 40]. In about half of the studies (17/32), screening was organized (i.e., using an invitation system) [17, 25, 26, 30-43]. In three quarters of the studies (24/32), information on HRT use was collected by self-report [14, 16-18, 20, 22, 24, 25, 27-30, 34-44, 46], and 63% (20/32) of studies collected screening participation by self-report [14, 16, 18, 20, 22, 24, 25, 27, 28, 30, 32, 34, 35, 37, 40-42, 44-46]. A more objective kind of information (medical or database records) on both HRT use and screening participation was available in 19% (6/32) of the studies [19, 21, 23, 26, 31, 33]. In the following summary of the results, statistical significance of an association (odds ratio or risk ratio) is only explicitly stated if the association was not significant.

Table 1 shows studies from the USA and Canada. All but one of the studies conducted in the USA showed a positive association of HRT use with participation in mammography screening [14, 16-22, 24-28]. In seven of the ten studies reporting an odds ratio (OR) or relative risk (RR), the odds of participating in mammography screening were at least twice as high among HRT users compared to non-users. The only study from the USA using exclusively data from 2002 or later was the one that showed the strongest association [28]: The odds of recent participation in mammography screening were four times higher in current vs. never users of HRT. One of two studies from the USA conducted in the context of an organized screening program [17, 25] found 100% increased odds of screening participation among users of HRT [25]. In 67% of studies (6/9) from the USA, absolute

differences in the prevalence of mammography screening according to HRT use or in the prevalence of HRT use according to screening participation were ≥ 10 percentage points.

The two studies from Canada only used data collected before 2002. One study conducted in an organized screening setting reported a 10% increased likelihood of participation among current HRT users [30], while the other study conducted in an opportunistic screening setting reported no difference in prevalence of HRT use between participants and non-participants [29].

Table 1 Studies from North America providing information on the association between use of hormone replacement therapy (HRT) and mammography screening, ordered by years of data collection

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results ^a
USA							
Joffe (2001), USA ^b [14]	n=69,445 Age: <55-65+ years	1988-1994	Opportunistic	Self-report (questionnaire) Categorization: Current vs. no current use	Self-report (questionnaire) Definition of participation: On-schedule screening ^c	Prevalence of (re-) participation	Current HRT use: 90.6% No current HRT use: 82.4%
Cook (2009), USA ^b [16]	n=55,625 Age: 40-69 years (mean 53.9 years)	1988-2000	Opportunistic	Self-report (questionnaire) Categorization: a) Current vs. never use b) Past vs. never use	Self-report (questionnaire) Definition of participation: On-schedule screening	Prevalence of ever HRT use (at baseline in 1988) Participation given HRT use	Participants: 58.3% Non-participants: 37.5% Current estrogen + progesterone: OR 3.3 [3.2-3.5] Current estrogen only: OR 2.6 [2.5-2.8] Past estrogen + progesterone: OR 2.0 [1.9-2.2] Past estrogen only: OR 1.5 [1.4-1.6]

^a Numbers in brackets denote the 95% confidence interval.

^b Joffe (2001) and Cook (2009) use the same data source with a different research question and new results.

^c On-schedule screening was defined as at least one screening exam in the following year or following two years after both a mammogram and clinical breast examination.

Table 1 (continued)

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results^a
Burman (1999), USA ^b [17]	n=5,059 Age: 40-70+ years	1989-1995	Organized	Self-report (questionnaire) Categorization: Ever vs. never use	Medical records Definition of participation: On-schedule screening	On-schedule screening given HRT use	OR 1.1 [1.0-1.3] ^c
Ruffin (2000), USA [19]	n=2,228 Age: 40-50+ years	1993-1994	Opportunistic	Medical records Categorization: Current vs. no current use	Medical records Definition of participation: Screening in the last year or the last 2 years	Participation given current HRT use	Screening in the last year: OR 1.9 [no confidence interval reported] ^{c, d} Screening in the last 2 years: OR 2.5 [no confidence interval reported] ^{c, d}

^a Numbers in brackets denote the 95% confidence interval.

^b Burman (1999) and Buist (2012) use the same data source with a different research question and new results.

^c Adjusted result. Burman (1999): False-positive index mammogram, age at index mammogram, first-degree relative with breast cancer, age at menarche ≤10 years, no childbirth before age 30 years, age at menopause ≥55 years, number of mammograms before index mammogram, false-positive mammogram before index mammogram. Ruffin (2000): Age, insurance type, number of visits to the practice in last two years, years as a patient, marital status, health maintenance examination.

^d Ruffin (2000) report no confidence interval, but significance is indicated in the publication (level of significance not stated).

Table 1 (continued)

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results ^a
Edwards (2009), USA ^b [20]	n=79,899 Age: 45-75 years (mean 59.2 years)	1993-1998	Opportunistic	Self-report (questionnaire) Categorization: a) Current vs. never use b) Past vs. never use	Self-report (questionnaire) Definition of participation: Annual or biennial screening	Prevalence of HRT use Annual participation given HRT use Annual or biennial participation given HRT use	Annual participation: 40.6% (current), 17.0% (past) No annual participation: 24.9% (current), 18.0% (past) Annual or biennial participation: 38.0% (current), 17.0% (past) No annual / biennial participation: 23.8% (current), 18.2% (past) Current use: OR 2.15 [2.07-2.24] Past use: OR 1.33 [1.27-1.39] Current use: OR 2.08 [2.00-2.16] Past use: OR 1.31 [1.25-1.36]
Rahman (2005), USA ^b [21]	n=20,389 Age: 40-70+	1994-1998	Opportunistic	Database record Categorization: Current vs. no current use	Database record Definition of participation: ≥2 mammograms within one year (age ≥50) or ≥2 mammograms within 2 years (age 40-49)	Prevalence of HRT use	Participant: 51.7% Non-participant: 47.1%

^a Numbers in brackets denote the 95% confidence interval.

^b This study included women <50 years/possibly premenopausal women (no age-adjusted result available).

Table 1 (continued)

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results^a
Newell (2001), USA [22]	n=1,424 Age: 67-101 years (mean 75.1 years)	1995-1996	Opportunistic	Self-report (face-to-face interview) Categorization: Current vs. no current use	Self-report (face-to-face interview) Definition of participation: Ever vs. never participation	Prevalence of HRT use Current HRT use given participation	Participants: 6.7% Non-participants: 1.3% OR 3.7 [1.7-8.4] ^b
Harvey (1999), USA [23]	n=1,133 Age: 32-90 years	1996	Opportunistic	Medical records Categorization: Current vs. no current use	Medical records Definition of participation: Screening mammogram in 1996	Number of screening mammograms	Current HRT use: 77 per 100 women (33 diagnostic mammograms per 100 women) No current HRT use: 84 per 100 women (24 diagnostic mammograms per 100 women)
Otero-Sabogal (2003), USA [24]	n=977 Age: 40-74 years	1996	Opportunistic	Self-report (telephone interview) Categorization: Ever vs. never use	Self-report (telephone interview) Definition of participation: Mammogram within 2 years prior interview and ≥3 mammograms in the past 5 years	Prevalence of HRT use Participation given HRT use	Adherent: 44.1% Non-adherent: 15.4% OR 2.7 [1.9-3.8] ^b

^a Numbers in brackets denote the 95% confidence interval.

^b Adjusted result. Newell (2001): Age, income, years of education, marital status, living alone, language of interview. Otero-Sabogal (2003): Age, foreign-born, years living in the United States, years of education, employment status, marital status, income level, health insurance, regular place of care, hysterectomy, church attendance, acculturation, medical care access difficulty, attitude towards physicians, familism, cancer-related fatalism, social network, city of residence.

Table 1 (continued)

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results ^a
Bobo (2004), USA [25]	n=1,685 Age: 50-69 years	1997-2000	Organized	Self-report (telephone interview)	Self-report (telephone interview) and medical records	Prevalence of HRT use	Participation after 30 months: 38.9% (before index mammogram), 10.2% (after index mammogram)
				Categorization: a) Ever before index mammogram vs. never use b) Use only after index mammogram vs. never use	Definition of participation: On-schedule screening		No participation after 30 months: 26.1% (before index mammogram), 7.2% (after index mammogram)
						(Re-)participation after 30 months given ever HRT use	OR 1.94 [1.30-2.91] ^b
						(Re-)participation after 30 months given HRT use after index mammogram	OR 1.81 [0.97-3.38] ^b

^a Numbers in brackets denote the 95% confidence interval.

^b Adjusted result. Bobo (2004): Race and ethnicity, education, moved since index mammogram, health status one year after index mammogram, had a hysterectomy, history of breast cancer, believed eligible for a free examination one year after index mammogram, has usual source of care, number of mammograms prior to index mammogram, received a reminder to rescreen, social support for rescreening from physician or nurse, social support from other source, program (state), sampling weights.

Table 1 (continued)

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results ^a
Buist (2012), USA ^b [26]	n=163,490 Age: 50-79 years	1998-2009	Organized	Administrative database Categorization: a) Current use (within 2 months) b) Never use (no use within 48 months)	Medical records and claims data Definition of participation: Screening within last 26 months	Prevalence of participation	Current estrogen-progestin use: 1998: 80.5%, 2003: 80.6%, 2009: 73.8% Current estrogen use: 1998: 75.0%, 2003: 77.2%, 2009: 76.9% HRT non-use: 1998: 51.9%, 2003: 58.1%, 2009: 59.9%
Otero-Sabogal (2004), USA [18]	n=1,023 Age: 50-65+ years	1999	Opportunistic	Self-report (telephone interview) Categorization: Current vs. no current use	Self-report (telephone interview) Definition of participation: Screening 10-18 months after first screen and ≥3 mammograms within past 5 years	Participation given HRT use	OR 1.9 [1.4-2.6] ^c

^a Numbers in brackets denote the 95% confidence interval.

^b Buist (2012) and Burman (1999) use the same data source with a different research question and new results.

^c Adjusted result. Otero-Sabogal (2004): Years living in United States, Pap test following guidelines, site has conducted in-reach activities, site offers other screening services, doctor-patient communication, decisional balance*years of schooling (interaction term; decisional balance refers to a summary measure of the difference between facilitators and barriers to obtaining mammogram.)

Table 1 (continued)

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results ^a
Borrayo (2009), USA [27]	n=2,231 Age: 40-79 years	2000-2005	Opportunistic	Self-report (computerized interview) Categorization: Current vs. no current use	Self-report (computerized interview) Definition of participation: First screen <51 years and interval to next screen ≤2 years	Prevalence of HRT use Participation given current HRT use	Adherent: 76.0% Non-adherent: 59.4% Non-Hispanic white women: OR 2.2 [1.7-2.9] ^b Hispanic women: OR 2.3 [1.6-2.2] ^b
Cui (2007), USA [28]	n=27,090 Age: 42-79 years	2002-2006	Opportunistic	Self-report (questionnaire) Categorization: a) Current vs. never use b) Former vs. never use	Self-report (questionnaire) Definition of participation: a) Screening within last 2 years vs. never screening b) Screening within last 2 years vs. past screening (screened but not within last 2 years)	Participation vs. never participation Participation vs. past participation	Current use: OR 4.1 [3.3-5.0] ^b Former use: OR 2.5 [2.2-2.9] ^b Current use: OR 2.1 [1.9-2.5] ^b Former use: OR 1.3 [1.2-1.4] ^b

^a Numbers in brackets denote the 95% confidence interval.

^b Adjusted result. Borrayo (2009): Age, study center. Cui (2007): Race, age at interview, education, marital status, household annual income, employment, health insurance, family history of breast cancer, age at menarche, age at first live birth, menopausal status, use of alcohol, BMI, smoking, medical visit within the past two years.

Table 1 (continued)

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results ^a
Canada							
Beaulieu (1996), Canada [29]	n=149 Age: 50-69 years	1991-1992	Opportunistic	Self-report (telephone interview) Categorization: History vs. no history of HRT use [no details reported]	Medical records Definition of participation: Adhering to prescription for screening	Prevalence of HRT use	Participants: 20.0% Non-participants: 20.5%
Bancej (2005), Canada [30]	n=873 Age: 50-69 years	1994-1999	Organized	Self-report (telephone interview) Categorization: Current vs. no current use (baseline)	Self-report (telephone interview) Definition of participation: On-schedule screening	Participation given HRT use	2 years after baseline: RR 1.09 [1.03-1.14] ^b 4 years after baseline: RR 1.09 [1.01-1.19] ^b

^a Numbers in brackets denote the 95% confidence interval.

^b Adjusted result. Bancej (2005): Age.

Table 2 shows studies from Europe, all of which were conducted in an organized screening setting [31-39]. Each of the three studies from the UK used data collected before 2002 only [31-33]. Two of these studies reported a 55–76% higher prevalence of HRT use among screening participants compared to non-participants [31, 33]. Both studies from France, one conducted before 2002 and one in 2005, showed an association between HRT use and participation in mammography screening [34, 35]. One study reported a prevalence of HRT use of 82% among screening participants vs. 13% among non-participants [34]. Compared to non-participants, Duport et al. found almost twofold increased odds for current HRT use among participants of organized mammography screening, and threefold increased odds among women undergoing (opportunistic) screening outside the program [35]. Of the two studies from Spain [36, 37], one study reported a 5% increase in the odds of screening re-attendance among current HRT users compared to current non-users [36]. The second study (including only 280 non-participants) reported decreased odds for HRT users to participate for the first time in the organized screening program, while the odds of having been screened outside the program were five times higher among HRT users [37]. The prevalence of HRT use among first-time participants was 16 percentage points lower compared to never participants. The two studies from Sweden reported a positive association regarding ever HRT use and screening participation [38, 39], which was not statistically significant in one study [39]. Overall, in 63% (5/8) of the studies from Europe reporting prevalences, the absolute difference in prevalence of mammography screening according to HRT or in the prevalence of HRT use according to screening participation was ≥ 10 percentage points.

Table 2 Studies from Europe providing information on the association between use of hormone replacement therapy (HRT) and mammography screening, ordered by years of data collection

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results ^a
United Kingdom							
Seeley (1994), UK [31]	n=1,309 Age: 50-64 years	1992-1993	Organized	Medical records Categorization: Current vs. no current use	Medical records Definition of participation: Screening between 1992-1993 or earlier	Prevalence of HRT use	Participants: 23% Non-participants: 13%
Lancaster (1995), UK ^b [32]	n=1,839 Age: 45-64 years	1993	Organized	Medical records and self-report (questionnaire) Categorization: Current vs. no current use	Self-report (questionnaire) Definition of participation: Mammogram at age >50	Prevalence of participation	Hysterectomized HRT users: 84% Hysterectomized HRT non-users: 84% Not hysterectomized HRT users: 83% Not hysterectomized HRT non-users: 76%
Banks (2002), UK [33]	n=1,064 Age: 49-60+ years (mean 57.4 years)	1998	Organized	Medical records Categorization: a) Ever vs. never use b) Current vs. no current use	Medical records Definition of participation: Screening ≤6 months after invitation	Prevalence of HRT use	Participants, ever use: 42% Non-participants, ever use: 27% Participants, current use: 32% Non-participants, current use: 19%

^a Numbers in brackets denote the 95% confidence interval.

^b This study included women <50 years/possibly premenopausal women (no age-adjusted result available).

Table 2 (continued)

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results ^a
France							
Flamant (2006), France [34]	n=7,852 Age: 50-65 years	1990-1997	Organized	Self-report (questionnaire) Categorization: Current vs. no current use	Self-report (questionnaire) Definition of participation: Screening at baseline and at all four follow-ups vs. screening neither at baseline nor at any follow-up	Prevalence of HRT use	Adherent: 82% Non-adherent: 13%
Duport (2008), France [35]	n=5,294 Age: 50-74 years	2005	Organized and opportunistic	Self-report (questionnaire) Categorization: Current vs. no current use	Self-report (questionnaire) and medical records Definition of participation: Screening within last 2 years vs. never/not on schedule screening	Prevalence of HRT use Participation given current HRT use	Opportunistic screening: 23.7% Organized screening: 16.3% No participation: 9.9% Organized (vs. never): OR 1.8 [1.3-2.4] ^b Opportunistic (vs. never): OR 2.8 [2.1-3.8] ^b

^a Numbers in brackets denote the 95% confidence interval.

^b The odds ratio for participation in organized and opportunistic screening (vs. never participation) was calculated using the data available in table 2 of Duport (2008).

Table 2 (continued)

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results ^a
Spain							
Román (2011), Spain [36]	n=1,371,218 Age: 44-69 years	1990-2006	Organized	Self-report (questionnaire)	Medical records	Prevalence of HRT use	Participants: 9.8% Non-participants: 6.9%
				Categorization: Current vs. no current use	Definition of participation: On-schedule screening	(Re-)participation given HRT use	OR 1.04 [1.03-1.06] ^b
Baré (2003), Spain [37]	n=13,965 (280 non-participants) Age: 50-64 years	1995-1998	Organized	Self-report (face-to-face and telephone interview)	Self-report (face-to-face and telephone interview)	Prevalence of HRT use	Participants: 6.0% Non-participants: 22.1%
				Categorization: Use vs. no use [no details reported]	Definition of participation: First-time participation vs. never participation	Participation given HRT use	OR 0.23 [0.17-0.30]
						Screened before first invitation given HRT use	OR 5.56 [4.35-7.14]

^a Numbers in brackets denote the 95% confidence interval.

^b Adjusted result. Román (2011): Age at screening, attended first invitation, menopausal status, previous invasive procedure, familial breast cancer, screening participation, screening period (years), radiology unit, interaction between false-positives and screening participation.

Table 2 (continued)

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results ^a
Sweden							
Lagerlund (2000), Sweden [38]	n=943 Age: 42-74 years (mean 55.8 years)	1988-1997	Organized	Self-report (questionnaire) Categorization: Ever vs. never use	Database record Definition of participation: ≥ 2 invitations and ≥ 1 screen	Prevalence of HRT use Participation given HRT use	Participants: 41.2% Non-participants: 22.6% OR 2.5 [1.8-3.3] ^b
Lagerlund (2013), Sweden [39]	n=4,666 Age: 44-72 years (mean 54.9 years)	1992-2009	Organized	Self-report (questionnaire) Categorization: a) Ever vs. never use b) Short vs. long-term use	Administrative database Definition of participation: Number of invitations attended vs. number of invitations not attended	Participation given HRT use	Ever HRT use: OR 1.10 [0.97-1.25] Long-term HRT use: OR 0.91 [0.71-1.16]

^a Numbers in brackets denote the 95% confidence interval.

^b Adjusted result. Lagerlund (2000): Age.

Table 3 shows the results from studies conducted in Australia, Brazil, and Taiwan. All three studies from Australia were conducted in an organized setting and based on data from 2001 or later. They showed two- to threefold higher odds of screening participation among users of HRT compared to non-users [40-42]. Two of the three studies from Australia reported absolute differences of ≥ 10 percentage points in the prevalence of HRT use according to screening participation or mammography screening according to HRT use. All three studies from Brazil used data collected after 2002 [43-45] and reported a positive association between HRT use and screening participation. The strength of the reported association varied and was partly not statistically significant, and two studies included women starting at the age of 40 [43, 45]. In both studies from Brazil, the absolute difference in prevalence of HRT use according to screening participation was ≥ 10 percentage points. The study from Taiwan reported an 80% increase in the odds of screening participation among HRT users compared to non-users.

Subgroup analyses regarding the type of HRT (combined vs. estrogen-only) were conducted in two studies [16, 26]. Both reported higher participation in current users of combined as well as estrogen-only HRT compared to non-users, but the odds of participation were higher for combined HRT in the study by Cook et al. (OR 3.3 for current combined use vs. OR 2.6 for current estrogen-only use) [16]. The same pattern was observed in the study by Buist et al. for the years 1998 and 2003, but not for 2009 [26].

Additional information on included studies (such as study design and selected quality criteria) is available in Appendix D.

Table 3 Studies from other countries providing information on the association between use of hormone replacement therapy (HRT) and mammography screening, ordered by years of data collection

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results ^a
Australia							
Achat (2005), Australia [40]	n=2,974 Age: 50-71 years	2001	Organized	Self-report (telephone interview) Categorization: Current vs. no current use	Self-report (telephone interview) Definition of participation: a) Ever vs. never participation b) On-schedule vs. not on schedule participation	Prevalence of HRT use Ever participation given HRT use On-schedule participation given HRT use	Ever participants: 43.5% Never participants: 23.3% On-schedule participants: 44.0% Not on-schedule participants: 32.5% OR 2.9 [1.6-5.6] ^b OR 1.8 [1.3-2.5] ^b

^a Numbers in brackets denote the 95% confidence interval.

^b Adjusted result. Achat (2005): Age.

Table 3 (continued)

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results ^a
Australia							
Weber (2013), Australia [41]	n=94,546 Age: 50-70+ years	2006-2010	Organized	Self-report (questionnaire) Categorization: Ever vs. never use	Self-report (questionnaire) Definition of participation: Mammography only or both mammography and colon cancer screening within the last 2 years vs. neither type of screening	Prevalence of participation Participation given ever HRT use	Ever HRT use: 61.5% (mammography only), 20.0% (mammography and colon cancer screening), 15.7% (neither test) Never HRT use: 52.2% (mammography only), 13.6% (mammography and colon cancer screening), 30.8% (neither test) Mammography only: OR 2.1 [2.0-2.2] ^b Both mammography and colon cancer screening: OR 2.4 [2.3-2.5] ^b

^a Numbers in brackets denote the 95% confidence interval.

^b Adjusted result. Weber (2013): Age, family history of cancer, place of residence, highest qualification, employment status, income, health insurance status, married or living with a partner, non-english language spoken at home, country of birth, treated by a doctor in the past month, need help with daily tasks due to illness or disability, psychological distress level.

Table 3 (continued)

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results ^a
Beckmann (2013), Australia [42]	n=1,148 Age: 40-84 years	2012	Organized	Self-report (face-to-face interview) Categorization: Ever vs. never use	Self-report (face-to-face interview) Definition of participation: Ever vs. never participation	Prevalence of participation Ever participation given HRT use	Ever HRT use: 91.4% Never HRT use: 54.8% OR 3.7 [2.3-6.1] ^b
Brazil							
Caleffi (2010), Brazil ^c [43]	n=3,749 Age: 40-69 years (mean 51 years)	2004-2009	Organized	Self-report (questionnaire) Categorization: History of HRT use [no details reported]	Administrative database Definition of participation: Mean screening interval ≤18 months	Participation given HRT use	RR 1.07 [0.98-1.16]

^a Numbers in brackets denote the 95% confidence interval.

^b Adjusted result. Beckmann (2013): Age, education, income, metropolitan or rural residence, birth place, socio-economic position, tall stature, BMI, physical activity, alcohol risk, family history of cancer, breast biopsy/surgery, menopausal age, menarche age, nulliparous, age at first birth.

^c This study included women <50 years/possibly premenopausal women (no age-adjusted result available).

Table 3 (continued)

Author (Year), Country, [Reference]	Study population	Years of data collection	Type of screening	Assessment of HRT use	Assessment of screening participation	Outcome of interest regarding HRT use and screening participation	Results ^a
Romeiro Lopes (2013), Brazil [44]	n=456 Age: 45-69 years (mean 58.7 years)	2010-2011	Opportunistic	Self-report (questionnaire) Categorization: Current vs. no current use	Self-report (questionnaire) Definition of participation: Mammogram within last 2 years	Prevalence of HRT use Participation given current HRT use	Participants: 26.2% Non-participants: 6.4% OR 1.5 [0.9-2.7] ^b
Romeiro Lopes (2016), Brazil ^c [45]	n=525 Age: 40-70+ years (mean 55.3 years)	2013-2014	Opportunistic	Medical records Categorization: a) Current vs. no current use b) Past vs. no past use	Self-report (interview) Definition of participation: Annual vs. no annual screening	Prevalence of HRT use Participation given current and past HRT use	Participants: 20.8% (past), 6.3% (current) Non-participants: 10.4% (past), 5.0% (current) Current use of HRT: OR 1.3 [0.6-3.3] Past use of HRT: OR 2.3 [1.4-3.3]
Taiwan							
Wang (2014), Taiwan [46]	n=776 Age: 45-69 years	2012	Opportunistic	Self-report (questionnaire) Categorization: HRT use vs. no use [no details reported]	Self-report (questionnaire) Definition of participation: Regular mammography [no details reported]	Participation given current HRT use	OR 1.8 [1.1-2.7] ^b

^a Numbers in brackets denote the 95% confidence interval.

^b Adjusted result. Romeiro Lopes (2013): BMI. Wang (2014): Age, residence, educational level, birth history, breastfeeding, family history of breast cancer, employment status, family income, personal history of breast cancer.

^c This study included women <50 years/possibly premenopausal women (no age-adjusted result available).

4. Discussion

To the best of our knowledge, this is the first systematic review summarizing evidence on the association between HRT use and participation in mammography screening. In addition to demonstrating the compelling evidence regarding a higher screening participation among HRT users compared to non-users, this review provides interesting insights into details of this association, such as variation according to years of data collection, between-country variation and differences regarding the type of screening. In studies from all countries (94% of all studies), higher mammography screening uptake among HRT users compared to non-users was reported. In about 70% of studies reporting an odds ratio, this association was ≥ 2 . In 65% of studies reporting prevalences, the absolute difference in the percentage of participation to mammography screening according to HRT use or in the prevalence of HRT use according to participation was ≥ 10 percentage points.

Given the broad dissemination of the findings of the WHI trial, we expected the strength of the association between HRT use and mammography screening participation to increase after 2002, i.e. after publication of the trial's findings. We partly observed such a pattern, but our review also shows that self-selection according to HRT use was already rather common in studies using data collected before 2002. This could have different reasons. First, the increased risk of breast cancer associated with HRT use already shown by observational studies conducted before the WHI trial [2], may have led to risk awareness among physicians or patients prior to 2002. Second, the association between HRT use and mammography screening might not (only) be a specific effect resulting from increased risk awareness, but could also be due to an unspecific healthy user bias. This means that health conscious women—often also those with a higher socioeconomic status—are both more likely to use certain drugs (in this case HRT) and to utilize preventive services [47]. However, our review also revealed that there is a lack of recent data on the association between HRT use and participation in mammography screening. The most recent data were from 2013/2014 (Brazil) and 2012 (Australia and Taiwan), while almost all data in the North American studies were

collected before 2000. Only studies from four out of nine countries (Australia, Brazil, France, and Taiwan) used data collected exclusively after 2002.

With respect to differences between countries, we expected a stronger association in countries with opportunistic mammography screening compared to settings with an organized screening program given that an invitation system is expected to counteract self-selection. Although the comparison between countries needs to be interpreted with caution due to heterogeneity regarding data years and in some cases small number of studies per country, our review suggests some differences supporting this hypothesis. Overall, rather strong (positive) associations (up to fourfold increase in the odds of screening participation among HRT users) were observed in the USA where the vast majority of studies were conducted in an opportunistic setting. The few studies reporting weaker or statistically not significant associations were typically conducted in countries with organized screening. However, there were also studies conducted in organized programs that showed very strong associations such as the most recent study from Australia [42], suggesting that further country-specific factors play a role. It is also important to note that the association between HRT use and mammography screening may partly be underestimated in studies conducted in organized settings because HRT users may be more likely to have mammograms outside the program, as observed in the study by Duport et al. conducted in France [35] and the study by Baré et al. conducted in Spain [37].

Given the particular impact of combined HRT use on breast cancer risk, stratification by type of HRT (combined HRT vs. estrogen-only HRT) would be an important aspect of studies on the association between mammography screening uptake and HRT use, but only the studies by Cook et al. and Buist et al. conducted such subgroup analyses [16, 26]. Although the association was stronger for combined HRT, they reported a marked association for both types of HRT, suggesting that the association is only partially selective.

The findings of our review imply, among other things, that studies investigating the effect of HRT use on breast cancer incidence or mortality may be biased if participation in

mammography screening is not taken into account. With respect to breast cancer incidence as endpoint, the mechanisms causing the bias may be as follows: HRT users are more likely to participate in screening (selection bias) and once they participate in screening the likelihood of detecting cancers that would not have reached a clinical stage during the patient's lifetime (overdiagnosed cancer) is increased. Disentangling these two effects, i.e. selection bias and overdiagnosis, from each other seems hardly possible. The bias results in overestimating the risk of breast cancer among HRT users as do other biases discussed by Zahl and Mæhlen [48].

For breast cancer mortality as endpoint, there would be a bias because prognosis is expected to be better among screening participants due the higher proportion of early stages. Bringing attention to this issue seems relevant, because the observational extension study of the WHI trial, for example, reporting a statistically non-significant increase of 1.44 in breast cancer mortality among combined HRT users (number of breast cancer deaths: 61 in the intervention arm and 40 in the placebo arm), did not adjust for mammography screening uptake during follow-up [49]. It is also not clear whether a recent analysis of the Million Women Study on HRT use and breast cancer mortality adjusted for mammography screening uptake during the 20-year follow-up, although it may be less relevant in this study given that baseline recruitment occurred among mammography screening participants and the three-year follow-up data suggested a high longitudinal adherence irrespective of HRT use [50].

We identified some limitations in studies included in this review that may be avoided in future studies on this research question. A total of four of the fourteen studies including also younger women possibly not eligible for HRT use did not provide age-adjusted results [21, 32, 43, 45]. Depending on screening eligibility of these women and potential reasons to start HRT already at a younger age (e.g., women with oophorectomy), the association between HRT use and participation in mammography screening may have been distorted in a certain direction in these studies.

Furthermore, information in this review is partly limited due to incomplete reporting or suboptimal collection of data in original studies. For example, some studies did not provide information on the definition of HRT users and non-users, i.e., whether use referred to current or former use or whether non-use referred to never use or current non-use. Similarly, it was often not stated whether non-participation in screening referred only to never participation or also to no recent participation. Moreover, the distinction between screening and diagnostic mammograms was not always explicitly made and only a few studies reported on the type of HRT. We hope that this review will stimulate a more detailed data collection and reporting on HRT use and mammography in future studies.

Most of the included studies collected information on utilization of mammography by self-report. The sensitivity and positive predictive value of self-reported mammography use have been estimated at about 95% and 80%, respectively [51]. Information on the validity of self-reported HRT use is limited, but a German case-control study reported good agreement with medical records, particularly for current or ever continuous use of combined HRT [52]. Thus, we do not expect that the studies' findings would substantially change if non-self-reported information was available. This fact is confirmed by the studies exclusively using information from medical or database records, which showed a consistently higher mammography screening uptake among HRT users [19, 21, 23, 26, 31, 33]. Only one of these studies reported less screening mammograms among HRT users compared to non-users, but HRT users in that study had notably more diagnostic mammograms than non-users [23].

In conclusion, our review suggests that—despite some variation—there is an overall consistent and relevant association between mammography screening and HRT use across countries, calendar periods, type of screening, and type of HRT. This demonstrates and underlines the importance of collecting detailed information on HRT use and mammography screening in any study investigating risk factors or evaluating preventive measures for breast cancer. Our review also highlights the need for studies in the field from further countries and with more recent data.

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