Cohort Profile: The Danish nurse cohort

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Accepted 15 February 2011

How did the cohort come about?
From the 1970s to the mid-1990s, ~20–30% of Danish women between 55 and 65 years of age used hormone replacement therapy (HRT).1,2 It was primarily used to alleviate climacteric symptoms, but from 1980s the therapy was also used for prevention of osteoporosis and from the 1990s for prevention of cardiovascular diseases. The literature based on observational studies, primarily US studies, suggested a considerable risk reduction of osteoporotic fractures3 and coronary heart disease, whereas findings on the effect of HRT on breast cancer were inconsistent.4

In 1976, the US Nurses’ Health Study was established, comprising 121 700 female registered nurses, who were between 30 and 55 years of age. This cohort was originally established to assess risk factors for cancer and cardiovascular diseases, with a particular interest in effects of oral contraceptives, use of hormones, cigarette smoking and other lifestyle factors. Ever since, the participants have been followed every other year with a mailed questionnaire to update exposure information and information on illnesses diagnosed since the previous questionnaire.5,6

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Inspired by this US cohort of nurses, the Danish Nurse Cohort was established to examine the benefits and risks associated with HRT use in a European population.

Who is in the Danish cohort of nurses?
The Danish Nurse Organization (DNO) gave permission to use their membership register as a way to make contact with Danish nurses. The register includes nurses at work as well as retired nurses, and with an inclusion rate of ~95%, the register provides access to nearly all Danish nurses.

In 1993, a questionnaire was mailed to 23 170 female Danish nurses >44 years of age. Followed by two reminders, a total of 19 898 (86%) nurses replied with a completed questionnaire. The cohort was re-investigated in 1999 with an additional inclusion of 10 534 nurses, who in the meantime were >44 years of age. A total of 31 642 nurses were included in this round, where 24 155 (76%) completed the questionnaire. A third survey of the initial cohort from 1993 was carried out in 2009. Of the 15 322 nurses who replied in both 1993 and 1999, a total of 12 955 nurses were alive and could be contacted in 2009, and, of these, 11 114 (86%) returned a completed questionnaire. Figure 1 shows the number of participants and non-participants in the 1993, 1999 and 2009 surveys.

What has been measured?
In 1993, we collected information on socio-economic and working conditions, parents’ occupation, weight and height including weight at birth, lifestyle (diet habits, smoking habits, alcohol consumption and leisure time physical activity), self-reported health (SRH), own history of various diseases, family history of cardiovascular and cancer disease and of fractures. Also, an extensive reproductive history including age of menarche, age of menopause, use of oral contraceptives and removal of uterus and ovaries were included. In the 1999 questionnaire the same information was collected, but since overweight and obesity had become an increasing health problem a new section was added to collect information on weight and weight change throughout the lifetime, including information of waist circumference. In 2009, this section was expanded with additional questions on weight loss methods. Overview of the main areas of information collected at the three surveys is shown in Figure 2.
Ascertainment of hormone therapy use among Danish nurses

Information on use of hormone therapy was self-reported. In 1993, a total 19,424 nurses gave information on systemic use of hormone therapy (HT). This information was classified as current, past or never use of hormones, and current use was subdivided into use of oestrogen alone and oestrogen combined with progestin. Overall, 6,673 (33%) had ever used HRT, 3,864 (20%) were still using it and 2,509 (13%) had used it in the past. We found that fewer Danish nurses used HRT compared with women from the Nordic Countries and from the UK.\textsuperscript{1,7} However, once the Danish nurses started to use hormones, they continued to use them for a long time—i.e. 57% continued to use HRT for 10 years, and after 15 years 48% of the women were still using HRT.\textsuperscript{8}

Use of HRT in 1993 was validated by comparing self-reported data with prescription data from two Danish counties, the Odense University Pharmacoepidemiological

Figure 1 Flowchart of participants and non-participants in the 1993, 1999 and 2009 surveys. \textsuperscript{a}Re-invited participants; \textsuperscript{b}new invited participants and \textsuperscript{c}non-responders in 1993 and re-invited in 1999
The sensitivity and specificity of self-reported current use in 1993 were 78.4 and 98.4%, respectively. Overall, the study found a relatively high validity of self-reported data on HRT use, including type of regimen and duration of treatment. 9

Ascertainment of outcomes
All disease-related outcomes were ascertained through national registries such as the Danish National Hospital Registry, 10 the Danish Cancer Registry 11 and the Danish registries of causes of death. 12

What has been found?
After an observation period of 6 years from 1993 to 1999, three main studies were carried out to examine the effect of HRT on ischaemic cardiovascular diseases, breast cancer and osteoporotic fractures.

HRT and risk of ischaemic heart disease and stroke
During the observation period, 351 cases of ischaemic heart disease (IHD) occurred (46 fatal and 305 non-fatal). Women currently on HRT were not better protected against IHD in general [hazard ratio (HR) 1.24; 95% confidence interval (CI) 0.94–1.65], neither were they protected against IHD classified as myocardial infarction (HR 0.93; CI 0.57–1.65) than those never on HRT: however, the effect of treatment was modified by diabetes. Current users of HRT with diabetes had an increased risk of IHD (HR 4.15; CI 1.38–12.45) and of myocardial infarction (HR 9.15; CI 2.02–41.44) compared with those who never had used HRT, but for ever (past and never) users with diabetes the risk was not significantly increased. 13
HRT and risk of stroke
A total of 144 cases of ischaemic or haemorrhagic stroke (99 cases were classified as ischaemic stroke and 45 as haemorrhagic stroke) occurred. Ever use of HRT was not associated with increased risk of stroke, but only among hypertensive women current use of HRT was associated with increased risk of stroke (HR 2.35; CI 1.16–4.74). This association was not found in normotensive women using HRT.14

HRT and risk of breast cancer
A total of 244 women developed breast cancer during the follow-up. An increased risk of breast cancer was found for current use of oestrogen alone [risk ratio (RR) 1.96; CI 1.16–3.35], for the combined use of oestrogen and progestin (RR 2.70; CI 1.96–3.73) and for current use of tibolone (RR 4.27; CI 1.74–10.51) compared with never use of HRT. In current users of combined HRT oestrogen with progestin, the continuous combined regimens were associated with a higher risk of breast cancer than the cyclic combined regimens.15

HRT and risk of fractures
During 40 190 post-menopausal person-years, 335 low-energy hip (28), wrist (265) and upper arm (54) self-reported first fractures occurred. The fracture incidence was significantly lower for current users (4.4 per 1000 person-years) than for never users of HT (9.2 per 1000 person-years) and for past users (11.6 per 1000 person-years for past users). Current users of HRT had an overall lower risk of fracture (HR 0.51; CI 0.37–0.69), but the protective effect of HRT was restricted to women who had used the therapy for >10 years (HR 0.27; CI 0.14–0.51). However, this protective effect ceased when the women discontinued the treatment regardless of duration of therapy and time since discontinuation.16 Fracture history in this study was obtained by questionnaires. In a validation study, where self-report fracture data were compared with registry-based data, we found that the positive predictive value for specific hip fractures was 88.6%, and upper arm and wrist 75.0 and 53.7%, respectively.17

Contrary to other observational studies we found that:

- HRT had no protective effect on IHD, and women with diabetes who currently used HRT had an increased risk of IHD;
- all types of the European traditional HRT regimens were associated with increased risk of breast cancer; and
- only long-term use of HRT offered protection against osteoporotic fractures.

Findings from our observational studies were in agreement with the findings from the US randomized controlled trial, the Women’s Health Initiative (WHI).18 Based on their findings, the WHI group recommends that HRT should not be used for primary prevention of chronic diseases in healthy post-menopausal women.

Influence of psychosocial work environment on women’s health
The cohort had data to address the influence of the work-related factors in relation to heart disease, breast cancer and overweight.

Psychosocial work environment and IHD
This study included 12 116 nurses, who in 1993 were actively employed (median age 51 years). During the 15 years of follow-up, a total of 580 incident cases of IHD were found (369 were angina pectoris, 138 were myocardial infarction and 73 other IHDs). Nurses who reported much too high work pressure in 1993 had a nearly 50% increased risk of developing IHD (HR 1.47; CI 1.14–1.88) and nurses who reported work pressure to be a little too high had an ~25% increased risk (HR 1.25; CI 1.04–1.50). When the study population was dichotomized according to years of age <51 and ≥51 years at baseline, the association between work pressure and IHD was strongest and only significant among the youngest women, suggesting that the effect of work pressure has a greater impact on the younger nurses.19 This study adds to the sparse literature that proposes a causal association between work stress and coronary heart disease among women.20

Psychosocial work environment and risk of breast cancer
Few studies have examined if chronic work-related stress is associated with development of breast cancer. A total of 455 women developed breast cancer during the 136 758 person-years of follow-up. Neither women with self-reported high work pressure (HR 1.17; CI 0.79–1.73) nor women with low influence on work organization (HR 0.98; CI 0.69–1.39) were at higher risk of breast cancer than other women with no such stressors. Work-related stressors did not affect breast cancer risk or prognostic characteristics of incident breast cancers at the time of diagnosis.21

Factors related to weight gain or weight changes
This study examined the influence of psychological workload on subsequent change in body weight from 1993 to 1999. Nurses who reported that they almost always were either too busy or never busy gained significantly more weight (3.1 and 3.5 kg, respectively) compared with nurses who reported to be busy only sometimes [2.5 kg (P = 0.04, 0.002)].22 This was particularly the case for nurses who were predisposed to obesity, i.e. having at least one obese parent. Predisposed nurses who were busy at work gained
4.4 kg, whereas other nurses gained only 3.2 kg. This suggests a synergy between predisposition to obesity and the psychological environment.23

Obesity and SRH are strong predictors of morbidity and mortality, but their interrelation is not well understood. This study showed that women who gained weight during the study period from 1993 to 1999 had higher odds of reporting poorer SRH (OR 1.18; CI 1.04–1.35), but weight loss among overweight nurses did not result in increase of SRH ratings.24 Further studies on the effect of weight changes are ongoing.

Psychosocial work environment and smoking cessation
The relationship between cigarette smoking and stress is complex and the mechanisms by which stress functions maintain addictive smoking behaviour are not well understood. In this study we found that nurses who reported some or much influence on their work were more likely to quit smoking compared with those who reported very little or no influence. We also found that nurses working only day shifts were more likely to quit smoking.25

Alcohol consumption and breast cancer and mortality
Only few studies have examined the association between frequency of drinking and risk of breast cancer. A linear relation was found between increasing alcohol intake and breast cancer, with 2% increased risk for each additional drink consumed (RR 1.02; CI 1.01–1.03). Weekend consumption and binge drinking (defined as intake of five or more drinks within 1 day) imply additional increase in breast cancer risk.26

Validation of a risk score to predict hip fractures
Data were used to validate a risk score to predict hip fractures in postmenopausal women developed by the WHI.18 The results showed that US algorithm was well calibrated on the Danish population, but the clinical utility of the WHI algorithm was limited by a low sensitivity at common decision thresholds and sub-optimal in non-HT users.27

Factors influencing the age of retirement among nurses
In Denmark, the publicly financed Old Age Pension is available at the age of 67 years (since 1999 it is 65 years for those born after July 1, 1939). In 1979, the post-employment wage (PEW) was introduced, making it possible to retire at the age of 60 years. This scheme, which is not conditional on health, has become the dominant path to early retirement. Approximately 40% of people at the age of 60–66 years received PEW benefits. A study based on data from the Danish Nurse Cohort was carried out to examine predictors of early retirement among nurses. At the age 61 years, about half of the nurses had left the labour market to receive PEW, and only 1 out of 10 would still be employed at the age 66 years. Poor SRH was a predictor for early retirement, but it should be noted that two out of three nurses, who considered their health to be good or very good, joined PEW. This indicates that nurses did not necessarily have a poor SRH when they decided to retire from work. Nurses living alone were more likely to remain at work to the general retirement age, whereas nurses having a retired spouse had an increased probability of early retirement. Furthermore, a relatively high income decreased the probability of early retirement indicating that financial circumstances play a role in the retirement decision.28

What are the main strengths and weaknesses?
The main strength of this cohort is the linkage of self-reported information of a lot of exposure variables to a range of nationwide registries by means of a personal identification number.

In 1968, all citizens alive and living in Denmark were assigned a unique and unambiguous identification number, and this number ensures accurate linkage to all national registers including the Danish National Hospital Register.29 Since 1977, it has been mandatory to collect data to this nationwide registry. It comprises data on all somatic hospital admissions with information on treatment and diagnoses, and, since 1995, information out-patient activities and emergency activities has been added.10 Other relevant registers are The Danish Cancer Registry and The Danish Registers of Causes of Death. The diagnostic information in these registries is classified according to the International Classification of Diseases (ICD-8) up to 1993, and from 1994 a corresponding national version of ICD-10 has been used.

Internal validity of data
It is well known that non-response is associated with ill health, and this was also the case in our study. During the follow-up period from 1993 to 1999, 4.5% of the primary responders died and 11% among the primary non-responders died. On the other hand, the high response rates obtained at all three surveys strengthened the internal validity of the data.

Selection bias
In the late 1990s, studies had shown that women with a better health profile were selected or selected themselves for HRT.30–32 and this questioned whether the preventive effect on coronary heart disease entirely could be attributed to HRT. In the Danish Cohort, we could not demonstrate that HRT users had a particular healthy lifestyle or better health.
On the contrary, nurses who had ever used HRT more often reported poor health than nurses who never used HRT. Also, a strong association between HRT and use of a variety of non-specific drugs such as analgesics, sleeping pills, sedatives, laxatives, herbal medicine and anti-hypertensive medicine could indicate that the women in our study have used HRT to alleviate general health problems, and we do not consider the so-called ‘healthy user effect’ could have biased our results.

External validity of the data
Nurses have been selected as a study population for large epidemiological studies due to high response rates and high degree of accuracy in filling out questionnaires, but this selection of the study population may impede the generalization of findings to a broader population.

To find out if nurses resemble the general female population in terms of lifestyle and health, we compared the study population in 1999 with a representative sample of the female Danish population using exactly the same measures. We found Danish nurses had a healthier lifestyle than other Danish women. They smoke less, have healthier eating habits and are physically more active during their leisure time; however, they consume more alcohol than other women. In spite of this healthier lifestyle, we could not show any other major health differences in terms of SRH, diseases and use of health-care facilities. Although Danish nurses have a healthier lifestyle than other Danish women, we believe that it is possible to generalize findings based on this cohort to a general female population.

Future plans
In 2009, when most of the cohort participants had left work, the focus of the study changed from midlife health issues to issues related to old age. The purpose of the follow-up is to identify factors associated with healthy ageing. For this reason we continued to collect information on lifestyle, body weight and health-related issues and added information on health-related quality of life using the SF-12® Patient Questionnaire (http://villagewellness.us/pdf/sf12.pdf). Furthermore, we collected information on mental stress using Sheldon Cohen’s Perceived Stress Scale (http://www.ncsu.edu/assessment/resources/perceived_stress_scale.pdf), and on the level of physical function using a scale developed to measure functional ability among elderly. Analyses of these data are ongoing.

Approval of the study
The establishment of the cohort was approved by The Scientific and Ethical Committee of Copenhagen and Frederiksborg Municipalities [J. no. (KF) 01-103/93], and the Danish Data Protection Agency [J. no. 1993-1110-1151].

Can I get hold of the data and where can I find more?
Please contact Torben Jørgensen, E-mail tojo@glo.regionh.dk, for more information, see our webpage at http://www.regionh.dk/fcfs.

Conflict of interest: None declared.

References


