UiT The Arctic University of Norway

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Number of children and risk of hormone receptor-positive versus hormone receptor-negative breast cancer

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Table of Contents

List of Tables

List of Figures

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Abstract

Introduction: With around 2.3 million cases, breast cancer became the most frequently diagnosed cancer in 2020 surpassing lung cancer cases and mortality. Based on histology and molecular characteristics, hormone receptor-positive (HR+) cancer has tumors with both estrogen and progesterone receptors. On the contrary, hormone receptor-negative (HR-) cancer has tumors not expressing estrogen or progesterone receptors. Getting pregnant before age of 30 years reduced the probability of disease by 50% compared to women who were childless.

Material and Methods: Data from the Norwegian Women and Cancer (NOWAC) cohort study from 1991 to 2018 was used. Based on the DAG diagram, our final survival model included the age of participants at the start of the study, their age at menarche, height, and the use of oral contraceptives. The Cox proportional hazards method was used to determine the effect of the number of children diagnosed with HR+ or HR- breast cancer. All demographic and lifestyle variables were compared with the number of children, breast cancer, and non-cases using the Chi-square test and one-way ANOVA test in the two descriptive tables.

Results: The multivariable analysis showed that multiparous women had a 26% lower risk of breast cancer (HR= 0.74, 95% CI: 0.65-0.85) while women with one or two children also had a 12 % reduced risk of breast cancer compared to the reference group (HR= 0.88, 95% CI: 0.78-1.01). The multivariable analysis of HR+ breast cancer showed women with multiple children had 34% lower risk (HR=0.66, 95% CI: 0.57-0.76) and women with one or two children had 16% decreased risk of HR+ breast cancer (HR=0.84, 95% CI: 0.72 - 0.96) compared to nulliparous women. Moreover, the multivariable analysis comparing with the reference group showed a greater risk of HR- breast cancer by 24% among women having multiple children (HR=1.24, 95% CI: 0.70 - 2.17) while women with fewer children had a 25 % greater risk of HR- breast cancer (HR=1.25, 95% CI: 0.72 -2.19).

Conclusion: In conclusion, having children was associated with a lower risk of breast cancer overall and hormone receptor-positive breast cancer diagnosis in Norwegian women. On the contrary, we have not observed the same association between the number of children and the risk of hormone receptor-negative breast cancer.

Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
CRN	Cancer Registry of Norway
DAG	Directed acyclic graph
ER-	Estrogen receptor-negative
ER+	Estrogen receptor-positive
HER2	Human epidermal growth factor receptor 2
HR	Hazard Ratio
HR-	Hormone receptor-negative
HR+	Hormone receptor-positive
HRT	Hormone replacement therapy
NOWAC study	Norwegian Women and Cancer study
PR-	Progesterone receptor-negative
PR+	Progesterone receptor-positive
TNBC	Triple-negative breast cancer

1. Introduction

1.1.Breast Anatomy

The breast is the mammary gland for women that is mainly used in lactation. It comprises of adipose tissues (fatty tissues) and epithelial cells that make up the lobules and ducts in the areola. Milk is stored in the lobules and then connected to the ducts. The nipple is an essential part of the breast where the ducts open (1) (Figure 1).

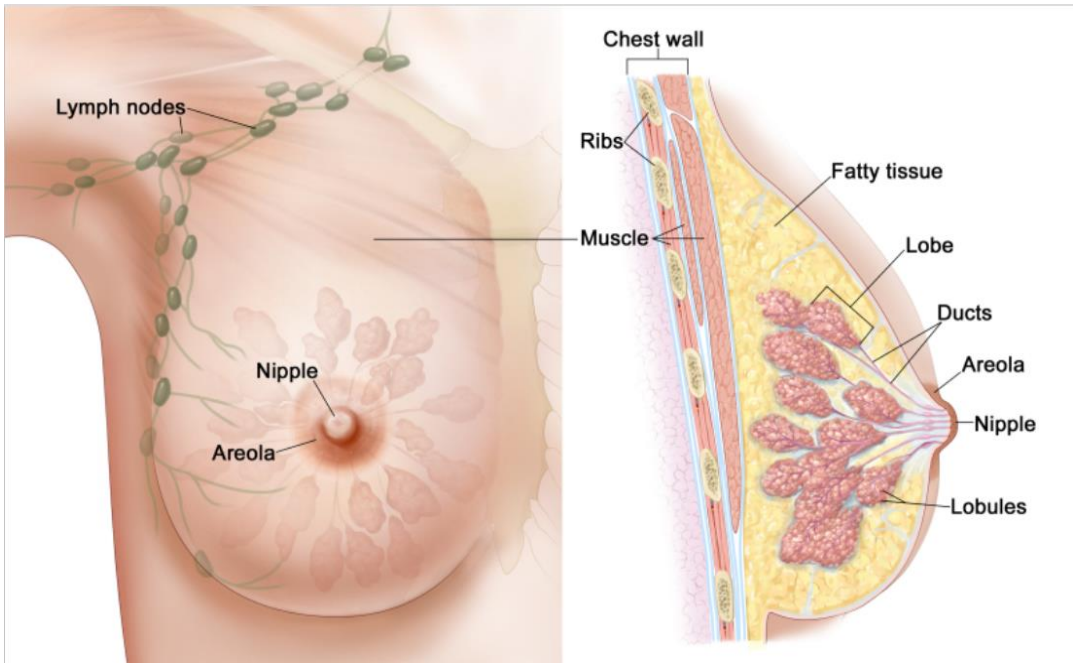


Figure 1: Anatomy of the human breast (2)

1.2.Breast Cancer Subtypes

Breast cancer can be defined as an abnormal growth of malignant cells inside mammary epithelial tissues (3). According to the early definitions, breast cancer is classified into two major types in situ breast cancer and invasive breast cancer. In situ is the carcinoma of epithelial cells present inside the breast lobules and breast ducts that have not invaded other cells or organs (4). Invasive cancer is known to spread from the site of origin to the remaining fatty, connective tissues up to the lymph system and even spread to other body parts (5).

In the year 2000, breast cancer was classified into four subtypes luminal A, Luminal B, basal-like or triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2 (HER2) tumors. These subtypes have diverse histology and differ in their disease prognosis or clinical outcomes (6).

Another way of classifying carcinomas is based on the size of the tumors. It is a powerful indicator of cancer prognosis because a smaller size (less than 1) tumor means a higher probability for patients to survive up to ten years (7). A molecular marker is any gene, protein or transcript whose amount can help determine the presence of cancer, its progression and the survival of patients (8).

Hormone receptors, Ki-67 antigen and HER2 are widely used breast molecular markers. A higher stain of Ki-67 antigen in tumors or lymph nodes indicates lower survival rates and the need for intensive medical care for patients. Likewise, the high presence of HER2 in breast tumors indicates an aggressive carcinoma with a higher chance of mortality as it cannot be managed through the use of anti-hormone therapy (8).

Proteins present inside the breast cells that can attach to the hormones are the hormone receptors (8). Since the mid-1970s, steroid hormone receptors like estrogen and progesterone receptors have been used in endocrine therapy and breast cancer diagnosis (9). Based on histology and molecular characteristics, hormone receptor-positive (HR+) cancer has tumors with both estrogen and progesterone receptors. On the contrary, hormone receptor-negative (HR-) cancer has tumors not expressing estrogen or progesterone receptors (6).

A significant proportion of breast cancer cases fall under HR+ tumors. It has less aggressive clinicopathological features and a favorable course of the disease. However, HR- breast cancer has a more aggressive disease progression (3). Because the progesterone receptor needs estrogen and estrogen receptors for its synthesis, the majority of estrogen receptor-positive (ER+) breast cancers are also progesterone receptor-positive (PR+) cancers and the estrogen receptor-negative (ER-) breast cancers are also progesterone receptor-negative (PR-) cancers. Therefore, very few cancer cases have single hormone receptors such as ER+ or ER- or PR+ or PR- (9).

1.3.Clinical Aspects

The backbone for the identification of breast tumors is mammography which examines breast lumps, changes in skin and nipple discharges. Although mammography has been a gold standard procedure in worldwide screening programs, magnetic resonance imaging has also become popular in diagnosing and treating cases. It is widely used when mammography becomes inconclusive and to understand the extent of cancer spread during diagnosis (10).

Over the years, surgery, chemotherapy, and radiation therapy are the treatment procedure for breast cancer. A popular treatment option has always been mastectomy which involves cutting off the human breast. However, numerous tumors today are treated by partial mastectomy or lumpectomy which is the removal of cancer tumors from the breast (11).

Medicines are also used to kill or shrink breast tumors. For HR+ cases, tamoxifen is given for 5-10 years to prevent cancer recurrence. On the other hand, HR- tumors are treated using chemotherapy. High-energy X-rays are targeted at a particular part of the breast, chest walls or lymph nodes. The whole breast is subjected to radiation therapy as part of breast-conserving therapy (11).

1.4.Global Epidemiology

Breast cancer is the most common form of cancer affecting women worldwide (6). Over 1.5 million women (25% of all women with cancer) are diagnosed with breast cancer every year throughout the world (12). According to Global Cancer Observatory (GLOBOCAN) 2020, breast cancer has a high prevalence of 7.7 million cases as shown in figure 2. With around 2.3 million cases, breast cancer became the most frequently diagnosed cancer in 2020 surpassing lung cancer cases and mortality(figure 3) (13). In the same year, there were 6.8 million deaths globally with 1 in 6 cancer deaths among women being attributed to breast cancer as shown in figure 4 (14).

In developed nations, 80% of cancer patients have survived up to five years. However, in the developing world which has a lack of early detection, diagnosis tools and treatment plans the survival chances are lower. The lowest survival rates are in the African region because around 77% of the cases are diagnosed at late cancer stages (15).

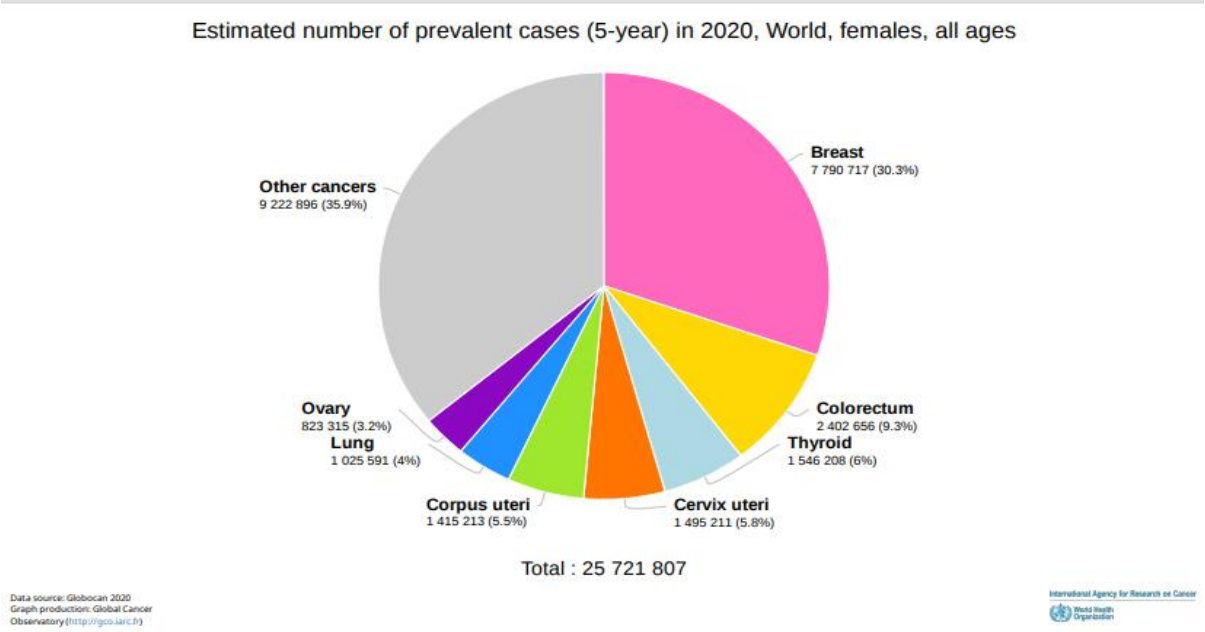


Figure 2: Global prevalence of breast cancer (13)

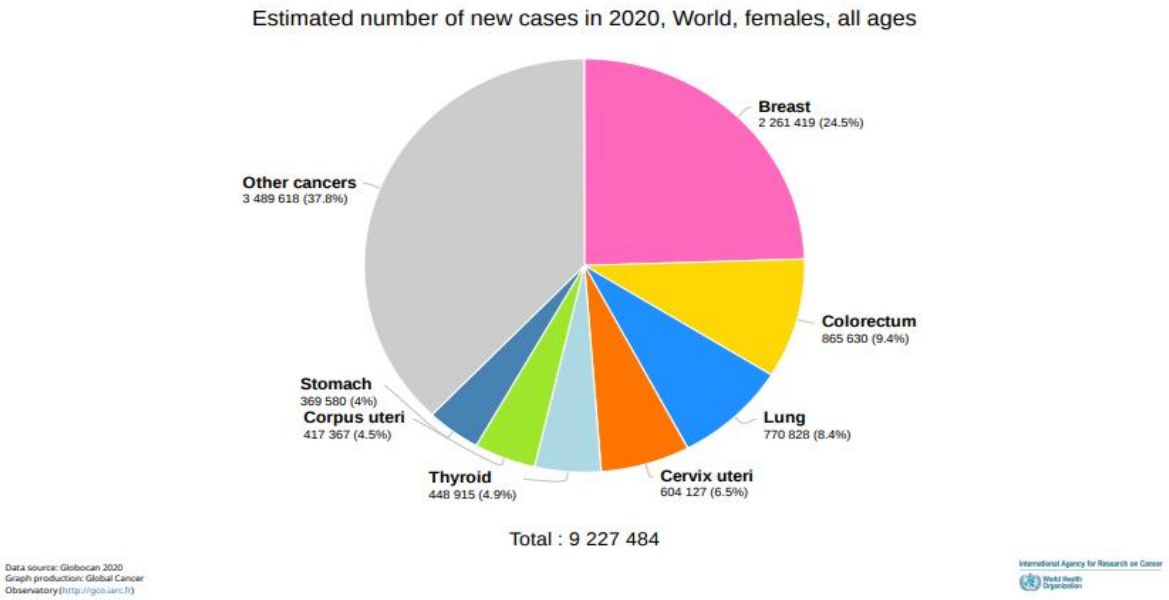


Figure 3: Global incidence of breast cancer (13)

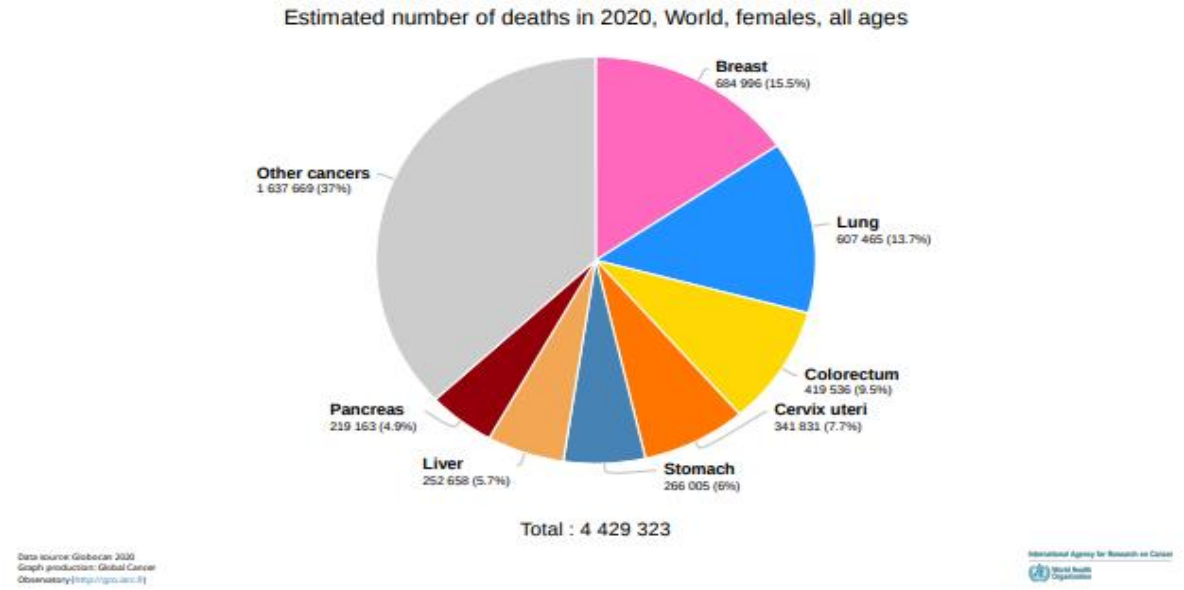


Figure 4: Global mortality of breast cancer (13)

Comparing global breast cancer incidence data from the last 30 years shows a dramatic rise in new cases by 128.32%. It is prevalent mostly in developed nations while low-income countries have fewer incident cases (16). Similarly, the mortality rate has also increased by 83.9% from 1990 to 2019 (16). High incidence and mortality after 1990 could be due to the establishment of national cancer registries that record accurate data on cancer cases within their population. Longer life expectancy among women has also contributed to higher incidence rates (17).

Although the increase in elderly populations and population growth have been key reasons for a rapid rise in cancer cases, the majority of developed countries also have prevailing risk factors for breast cancer (14).

1.5.Risk Factors

Breast cancer risk factors are either irreversible genetic aspects that cannot be altered or they are acquired from an individual's lifestyle (18). Epidemiological studies have shown that age at menarche, age at birth of the first child, number of children and breastfeeding are linked with the risk of HR+ breast cancers. On the other hand, well-defined risk factors for HR- tumors are still not clear. The known risk factors are mainly related to female sex hormones (19).

Gender plays a crucial role in breast cancer as women have a 100 times higher risk of getting diagnosed compared to men (19). Another aspect is the age of women as cancer is diagnosed after the age of 50 years or older. As about 10 % of cancer cases are related to the family, women have a higher chance of getting breast cancer if their first-degree relatives like their mother or sister have breast cancer (18). Various literatures have shown a linear dose-response relationship between women's height and breast cancer. Taller women have a higher probability of breast cancer as a 10-centimeter increase in height raises the cancer risk by 17 percent (20).

Age at menarche and menopause have influenced cancer incidence since menstruation is linked with exposure to estrogen and progesterone hormone. Menarche at an early age before 12 years or menopause later than 55 years will lead to additional menstrual cycles and extended exposure to both sex hormones throughout their lives. Because birth control pills or oral contraceptives are made up of female sex hormones, it can increase the probability of getting cancer (18).

The use of hormone replacement therapy (HRT) in postmenopausal women is associated with the increased incidence of breast cancer cases in cohort studies like the Million Women Study and the Norwegian Women and Cancer (NOWAC) study (21). For elderly women who have menopause, the fat tissues in their bodies are their source of estrogen. In obese women, additional fat tissues lead to an increase in estrogen levels and cause breast cancer (18).

Alcohol use is another risk factor with risk correlating to the amount consumed. Based on the level of alcohol consumption, women having more than three drinks daily have a greater chance of disease (18). Studies that link smoking with breast cancer have shown a higher cancer prevalence among smokers compared to non-smokers (22). However, smoking is not established as a risk factor for breast cancer according to the World Cancer Research Fund (23).

On the contrary, physical activity, breastfeeding and giving birth to multiple children can reduce risk (12). Women who breastfeed do not get their monthly periods for several months after their childbirth meaning breastfeeding reduces the exposure to sex hormones during menstrual cycles. Thus, studies conclude that the risk of getting breast cancer is minimized among women who breastfeed their child for one and a half or two years. Evidence from numerous meta-analyses has stated that regular physical activity reduces the risk of cancer. A possible explanation for this could be the correlation between body weight and physical activity (18).

1.6.**Number of children reduces breast cancer risk**

A crucial factor that can lower the risk of breast cancer in women is childbirth. Even though there are some arguments, breastfeeding has been linked with decreased risk as it correlates with giving birth. Understanding breast tissues, undifferentiated breast tissues have a higher chance of becoming malignant or cancerous compared to differentiated breast tissues. Women who have children have an increased proportion of differentiated lobular tissues than women without children (24).

The estrogen hypothesis estimates that women who are subjected to a higher amount of estrogen hormones over their lifetime have a higher probability of developing cancer in their breasts. However, this carcinomic effect does not affect women who have children as hormonal changes during pregnancy and the lactation period pause the exposure to estrogen (24). Moreover, breastfeeding is said to activate the process of cell differentiation and maturation of breast tissues. Therefore, parous women have a reduced risk of developing cancer in breast tissues (24).

Metabolism and gene expression profiles of carcinomas are directly influenced by hormones produced during pregnancy. Because these changes can greatly determine the risk of developing cancer, having more children can protect mothers from developing breast cancer. Getting pregnant before age of 30 years reduced the probability of disease by 50% compared to women who were childless (25).

1.7.Breast cancer in Norway

The Cancer Registry of Norway (CRN) established in 1952 is estimated to be 98% complete in recording information on cancer cases within the country. Similar to global data, breast cancer was the most common cancer affecting Norwegian women with 3726 new cases in 2019. Breast cancer incidence trends over the last 30 years show that the cases have doubled from 1990 to 2019 due to a dramatic increase in incidence from the mid-1990s up to 2005 (26).

This rising incidence was due to the implementation of the Norwegian Breast cancer screening Program which included a mammography test for women from age of 50 to 70 years. Norwegians are at a higher risk of getting breast cancer with the assumption that one in eleven women will be diagnosed before they reach old age. A significant proportion of cases have survived for five years or more due to advanced medical care and treatment plans (26).

1.8.Number of children in Norway

The fertility rate in Norway is higher compared to other European countries. A strong economy and benefits provided by State for childcare can be the major factors for the fertility rate to remain above 1.6 births. The increased use of contraceptives, marriage at a later age and pursuit of higher education have contributed to a decrease in fertility from the mid-1960s. Despite this, the majority of Norwegian women in the 1900s have given birth to an average of 2 children (27).

1.9. Directed acyclic graphs (DAGs)

A crucial part of epidemiological studies must be to identify confounders that can influence the effect of exposure on the outcome. A greater proportion of error can be omitted by the correct selection of confounding variables. DAGs are a commonly used medium that uses visual representation diagrams to convey information about the variables in any study. As the name suggests, the causal associations between variables are visually presented through directed arrows from cause to effect (28).

Since causality implies the cause must precede the effect, these graphs are acyclic. The exposure (E) and outcome (O) are the main variables in the diagram and the effect of exposure on outcome in a directed path is shown by the arrow. A confounder (C) is the variable linked to both exposure and outcome by a backward path. (E$\leftarrow$ C $\rightarrow$O) (28).

Moreover, the variable that is in the causal pathway between the exposure and the outcome is a mediator(M). It is presented by an arrow from the exposure to the mediator and then the causal path leads to the outcome (E → M → O). DAG provides a visual representation of the research topic to increase understanding among researchers and readers on which covariates control in the analysis to reduce bias (28).

1.10. The rationale for the study

Among the existing literature on the topic of breast cancer and parity, a substantial number of papers have been case-control studies with small sample sizes. The small sample size for subtypes of breast cancer cases reduces the power of the study and provides inconsistent conclusions. There have only been a handful of longitudinal studies which have assessed this topic, but they have shown inconsistent results (29, 30) (31-33).

Another aspect to consider is that several publications use diverse definitions for the molecular subtypes of breast cancer like as luminal A, luminal B and TNBC subtypes instead of hormone receptor-positive and hormone receptor-negative cancers (31). Research conducted in Norwegian populations have jointly assessed the risk of reproductive and lifestyle factors with molecular breast cancer subtypes (34). However, there is a lack of cohort studies in Norway that focus specifically on the protective effect of parity in HR+ versus HR- breast cancers.

1.11. Research question

What is the effect of the number of children on the risk of hormone receptor-positive breast cancer compared to hormone receptor-negative breast cancer?

2. Material and Methods

2.1. Study Design and Study Population

A prospective cohort study design was used to conduct this master thesis. The Norwegian Women and Cancer (NOWAC) cohort study that began in 1991 is a nationwide population-based cohort study. Around 320,000 women from age of 30 to 70 years were randomly sampled from the Norwegian Central Person Register. The unique national identity number was used to identify and link the participants with the CRN along with the Causes of death registry. This cohort is a representation of Norwegian women who were born between the years 1927 to 1965. The baseline questionnaire in the NOWAC study includes questions on women's reproductive history along with their dietary habits, lifestyle, medications, anthropometry, and self-reported diseases. The response rate for this cohort was 57 percent (35).

Figure 5 shows that the NOWAC study had information on 172,472 women that have been recruited from 1991 up to 2007. For this master thesis, we used the information from the dataset with a follow-up of twenty-seven years from 1991 to 2018.

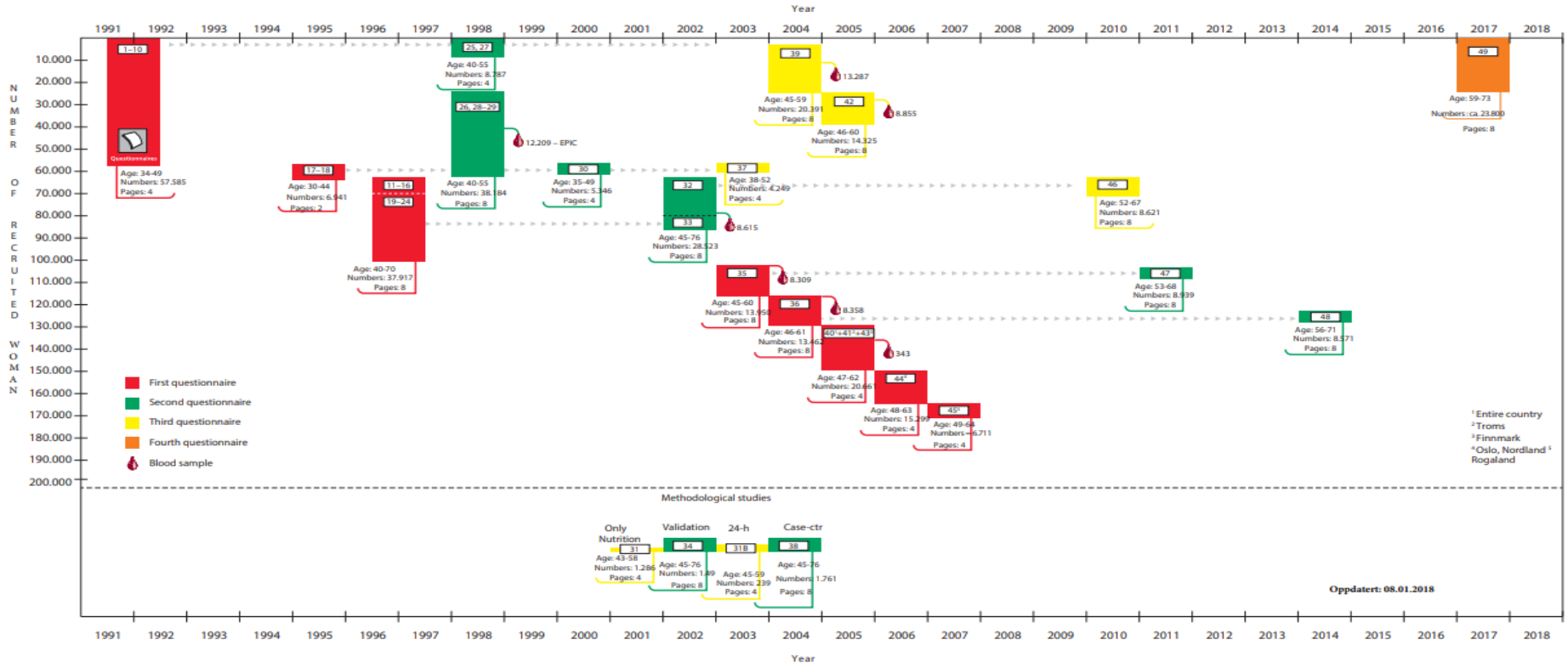


Figure 5: Timeline for NOWAC study follow-up

In the x-axis, we have years of follow up which began from 1991 up to 2018. The y-axis shows the number of women recruited in the cohort. The red boxes in the figure represent women who have answered the baseline questionnaire with green, yellow, and orange boxes showing women who have been followed up in the upcoming years.

2.2.Ethical Consideration

NOWAC study had received approval from both The Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. Participants within the cohort provided their written informed consent to record their information. The researchers did not have access to the personal identity number of participants as the dataset provided to them was anonymous. Statistics Norway had a special key that allowed researchers to connect participants from this NOWAC cohort to the CRN and Registry of Death in Norway(35).

2.3.Questionnaire data

Among the questions on reproductive history, women were asked about their number of pregnancies. The total number of children they have was self-reported by the participants at the beginning of the cohort study. This continuous variable was then made into a categorical variable for analysis. The three categories were women having “0 children”, “1-2 children” and “3 or more children”.

Education was classified into four categories based on the self-reported duration of education as follows “0-9 years of education”, “10-12 years of education”, “13-16 years of education” and “more than 17 years of education”. Age, weight, height, and duration of breastfeeding were self-reported by the participants and analyzed as continuous variables.

The self-reported height and weight of the participants were used to calculate their Body Mass Index (BMI). BMI variable was then coded into four categories based on the World Health Organization (WHO) definition of BMI. Participants having BMI less than 18.5 were classified as “underweight”, a BMI of 18.5 to 25 was “normal weight”, a BMI of 25 to 30 was “overweight” and d BMI of more than 30 was “obese”.

Among lifestyle variables, smoking at the baseline questionnaire was categorized into “never smokers”, “former smokers”, and “current smokers”. The questions on alcohol consumption focused on whether women drink alcohol or not. Physical activity in the questionnaire was measured on a 10-point scale starting at 1 which is a very low value while 10 is a very high value of physical activity. This variable was further grouped into three levels which are “low physical activity” (1-4 value on the scale), “medium physical activity” (5-7 value) and “high physical activity” (8-10 value).

Among reproductive variables, age at menarche and age at menopause were analyzed as continuous variables. Regarding the family history of breast cancer, the prevalence of breast cancer in their mother and the prevalence of breast cancer in their sister were included as “yes” or “no”. The use of oral contraceptives was divided into two categories those who “ever use” or “never use”. The study focused on the “ever use” or “never use” of HRT by participants.

2.4.Registry data

The two main outcome variables in this study were HR+ breast cancer cases and HR- breast cancer cases. Breast cancer cases were classified as C50 in the NOWAC study dataset based on the International Classification of Disease 10 (ICD-10). The breast cancer cases were identified by linking women from the NOWAC cohort to the CRN through their unique identity numbers.

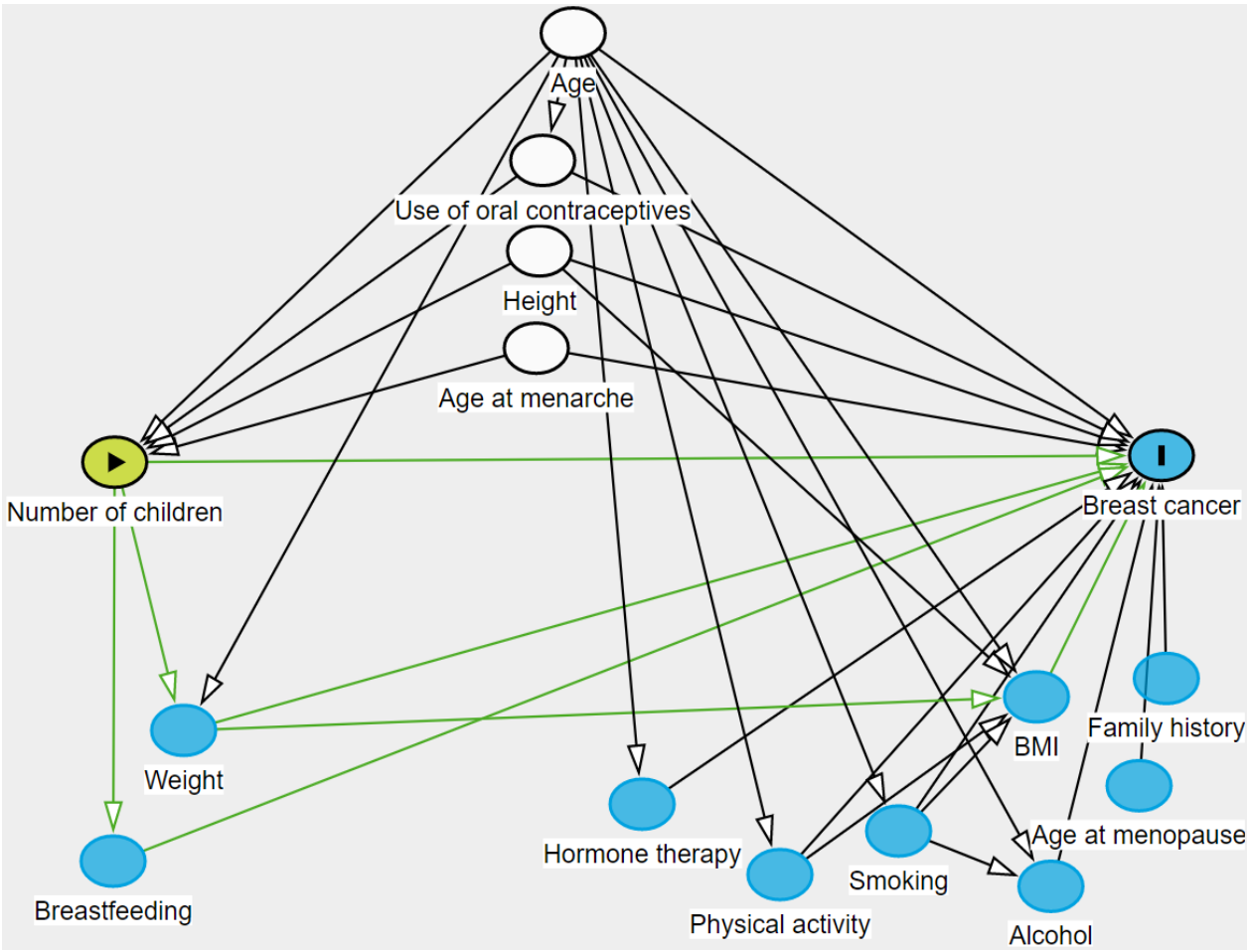
ER+ cases were defined as those with a tumor where >=1% of cells expressed the receptor. ER- cases were those with less than 1% of examined tumor cells expressing the receptor. PR+ cases were defined as those with a tumor where >=10% of cells expressed the progesterone receptor. Conversely, PR- cases had less than 10% of examined cells that expressed the receptor. HR+ breast cancer cases were those which were positive in both estrogen and progesterone receptors, or they were either ER+ or PR+. On the other hand, HR- breast cancer cases were those which had negative in both receptors (ER- and PR-).

2.5.Causal diagram and selection of covariates

To map out the potential causal relationship between the exposure, outcome and the third variables, we used a DAG. In figure 6, the exposure was the number of children, and the two outcomes (HR+ breast cancer and HR- breast cancer) were jointly placed as breast cancer along with the other variables in the study. Based on the review of previous literature, height, age, use of oral contraceptives, and age at menarche were confounders in this study as they were related to both the exposure and the outcome. In addition, they were not on the causal pathway between the number of children and breast cancer (36-39). Breastfeeding and weight were identified as mediators based on previous studies (40, 41).

Although the age at menopause, family history and use of HRT were risk factors for breast cancer, previous papers showed they were not associated with the exposure number of children (36, 42, 43). A review of existing literatures showed that smoking, drinking and being physically inactive before pregnancy was associated with the number of children (44, 45). However, in this study, we did not know if the participants started smoking, and drinking and were physically inactive from their teenage years or if these habits started after childbirth.

Based on the DAG diagram, our final survival model included the age of participants at the start of the study, their age at menarche, height, and the use of oral contraceptives.



= Exposure

= Outcome

= Adjusted ancestor of exposure and outcome (confounders)

= Ancestor of outcome

= Causal pathways

Figure 6: DAG showing a causal relationship between variables

2.6.Study sample

A total of 172,472 women who had completed the first baseline questionnaire were eligible for the study. Among these participants, 6696 women with a prevalent cancer diagnosis were excluded from this study. Moreover, 96,145 women having menstrual cycles were not eligible for this study.

Among the remaining 69,631 women, those who had missing values in height (n=1068), age, use of oral contraceptives (n=3625) and age at menarche (n=909) were excluded from the study to perform a complete case analysis. Figure 7 summarized the above information and showed that the study included a sample size of 64029 women.

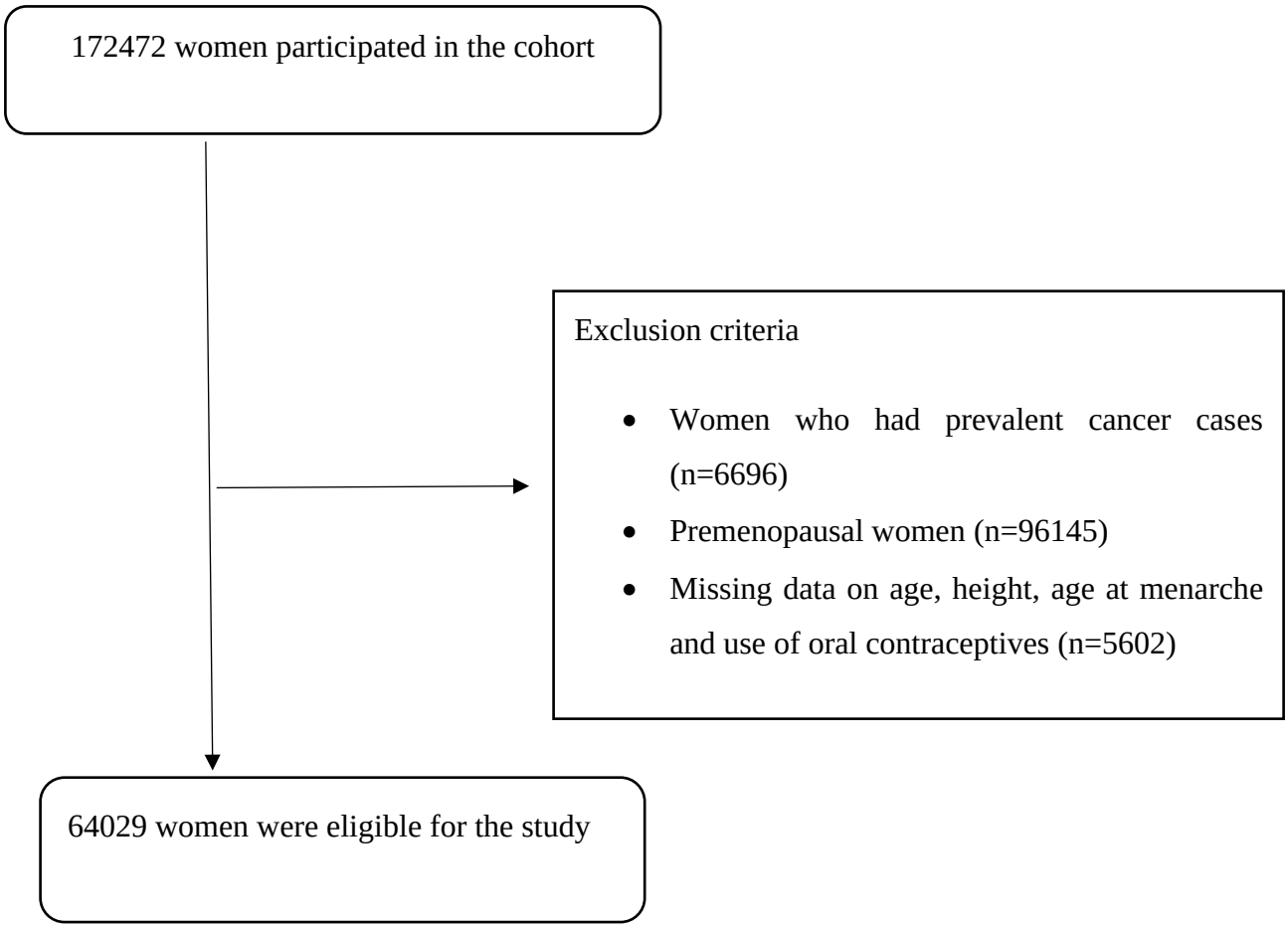


Figure 7: Flowchart of selection of study participants

2.7.Statistical Methods

All demographic and lifestyle variables were compared with the number of children using the Chi-square test and one-way ANOVA test in the first descriptive table (Table 1). The second descriptive table (Table 2) included the difference in baseline characteristics between breast cancer subtypes (HR+ and HR- cases) and those without breast cancer using the same statistical tests. Cox proportional hazards method was used to determine the effect of the number of children being diagnosed with HR+ or HR- breast cancer.

Log(-log) survival curves were used to assess the proportional hazard assumptions among breast cancer subtypes. For the timescale in the regression model, the age of participants was used. The follow-up time started from the time these participants answered the first questionnaire. Participants were followed until they were either diagnosed with any type of cancer, they died, migrated outside Norway or until the study ended on 31 December 2018.

In the survival model, there were three events of interest namely breast cancer, HR+ breast cancer, and HR- breast cancer. The variable breast cancer was the combination of women diagnosed with HR- cancer, HR+ cancer and other subtypes of breast cancer. The survival model for HR+ cases had an additional censoring of HR- cases with other subtypes of breast cancer. Similarly, the survival model for HR- cases censored HR+ cases alongside the other subtypes of breast cancer.

Hazard ratios (HR) with confidence intervals (CI) were used to approximate the relative risk. P-values below 0.05 were considered statistically significant. The age-adjusted part of the table was the univariable regression analysis. In the multivariable analysis, all four covariates were included in the survival model. Women having no children was the reference category among the three categories of exposure variable (number of children). A statistical analysis software named Statistical Package for the Social Sciences (SPSS) version 28 was used in the analysis of statistical data for this study.

3. Results

3.1.Descriptive characteristics among the number of children

Table 1 shows the difference in baseline characteristics between the different categories of the number of children. In the sample of 64,029 women, many had given birth to one or two children whereas only a few were nullipara. The mean age at menarche and menopause were similar among all categories of the number of children. Women who had more children had a lower level of education whereas a significant proportion of women without children had completed seventeen years of education.

While most of the participants with one or two children were former smokers, the majority of participants in the other two groups had never smoked before. Moreover, many women did not have a family history of breast cancer or use oral contraceptives or HRT. While comparing women with different number of children, differences in all the demographic characteristics were statistically significant. However, the actual difference between groups is small and with limited biological significance.

Table 1. Difference in demographic characteristics in relation to the number of children in the Norwegian Women and Cancer Study

	No Children	**1-2 Children**	**3 or more children**	**P-Values**
Total women (%)	5658 (8.8)	31930 (49.9)	26441 (41.3)	
Age*	56.4 (5.8)	56.1 (5.5)	57.3 (5.7)	<0.001
Height *	166.1 (6.3)	166 (5.7)	165.5 (5.6)	<0.001
Weight *	68.8 (13.2)	68.5 (11.7)	69.6 (11.9)	<0.001
Age at menarche*	13.3 (1.5)	13.4 (1.4)	13.4 (1.4)	<0.001

Age at menopause*	48.1 (5.6)	49 (4.8)	49.2 (4.5)	<0.001
Duration of breastfeeding*	0	7.8 (6.5)	16.9 (13.5)	0.000
BMI**				
Underweight	140 (2.5)	478 (1.5)	331 (1.3)	
Normal	3160 (56.7)	18183 (57.7)	13318 (51.1)	<0.001
Overweight	1557 (28)	9747 (30.9)	9209 (35.3)	
Obese	712 (12.8)	3111 (9.9)	3214 (12.3)	
Education**				
0-9 years	1074 (20.5)	6880 (23)	9263 (38)	
10-12 years	1489 (28.4)	10681 (35.7)	7595 (31.1)	0.000
13-16 years	1443 (27.5)	7932 (26.5)	5101 (20.9)	
More than 17 years	1242 (23.7)	4390 (14.7)	2441 (10)	
Use of oral contraceptives**				
Ever	2141 (37.8)	15850 (49.6)	10850 (41)	<0.001
Never	3517 (62.2)	16080 (50.4)	15591 (59)	
Use of HRT**				
Ever	2610 (47.8)	15237 (49)	10639 (41.4)	<0.001
Never	2854 (52.2)	15877 (51)	15030 (58.6)	

Smoking**				
Never	2284 (40.7)	10491 (33.1)	10487 (40)	<0.001
Former	1925 (34.3)	12443 (39.2)	8680 (33.1)	
Current	1399 (24.9)	8773 (27.7)	7039 (26.9)	
Alcohol Consumption**				
Yes	766 (14.6)	2338 (7.8)	3807 (15.6)	<0.001
No	4543 (85.4)	27647 (92.2)	20525 (84.4)	
Physical Activity**				
Low	1406 (27.1)	7400 (24.9)	5980 (25.3)	0.022
Medium	2896 (55.9)	17114 (57.7)	13555 (57.3)	
High	880 (17)	5170 (17.4)	4124 (17.4)	
Breast cancer in mother**				
Yes	376 (7.3)	1938 (6.5)	1460 (6.1)	0.002
No	4775 (92.7)	27673 (93.5)	22568 (93.9)	
Breast cancer in sister**				
Yes	230 (5.7)	1108 (4.6)	1034 (5)	0.003
No	3795 (94.3)	23062 (95.4)	19547 (95)	

Hormone receptor status**				
HR+ breast cancer	230 (94.3)	1123 (91.4)	783 (89.6)	<0.001
HR- breast cancer	14 (5.7)	105 (8.6)	91 (10.4)	

* Mean values in each children category with standard deviation in the brackets

** Number of participants in each children category with proportions in the brackets

3.2.Descriptive characteristics among HR+ cases, HR-cases, and non-cases

Table 2 shows the difference in baseline characteristics between breast cancer subtypes (HR+ and HR- cases) and those without breast cancer. Mean height and weight were higher among women who had been diagnosed with breast cancer. However, there was no difference in age at menarche and menopause among breast cancer cases and non-cases.

More of the HR- cancer cases had used oral contraceptives compared to the women in the other two groups. The use of HRT was higher in both HR+ and HR- breast cancers compared to non-cases. The differences between height, weight, education, number of children, use of HRT, physical activity, and family history of breast cancer were statistically significant.

Table 2. Difference in demographic characteristics between breast cancer cases (HR+ and HR- cases) and non-cases in the Norwegian Women and Cancer Study

	Non-Cases	HR+ Cases	HR- Cases	P-Values
Number of women (%)	61683 (96.3%)	2136 (3.3%)	210 (0.3%)	
Age*	56.6 (5.6)	56.5 (5.3)	55.8 (5.3)	0.059
Height*	165.8 (5.7)	166.5(5.6)	166.3 (5.7)	<0.001
Weight*	69 (11.9)	70.2 (11.7)	70.3 (11.3)	<0.001
Age at menarche*	13.4 (1.4)	13.3 (1.4)	13.2 (1.4)	0.053
Age at menopause*	49 (4.8)	49.2 (4.7)	49.1 (4.6)	0.272
Duration of breastfeeding*	12.8 (11.9)	12.2 (11)	12.1 (10)	0.329
BMI**				
Underweight	917 (1.5)	31 (1.5)	1 (0.5)	0.225
Normal	33446 (55)	1106 (52.5)	109 (52.2)	
Overweight	19723 (32.4)	714 (34)	76 (36.4)	
Obese	6759 (11.1)	255 (12.1)	23 (11)	

Education**				
0-9 years	16677 (29.1)	501 (25.4)	39 (20.2)	<0.001
10-12 years	19022 (33.2)	664 (33.6)	79 (40.9)	
13-16 years	13896 (24.2)	533 (27)	47 (24.4)	
Above 17 years	7767 (13.5)	278 (14.1)	28 (14.5)	
Number of children**				
0 children	5414 (8.8)	230 (10.8)	14 (6.7)	<0.001
1-2 Children	30702 (49.8)	1123 (52.6)	105 (50)	
3 or more children	25567 (41.4)	783 (36.7)	91 (43.3)	
Use of oral contraceptives**				
Ever	27741 (45)	994 (46.5)	106 (50.5)	0.103
Never	33942 (55)	1142 (53.5)	104 (49.5)	
Use of HRT**				
Ever	27263 (45.5)	1117 (53.9)	106 (52.7)	<0.001
Never	32710 (54.5)	956 (46.1)	95 (47.3)	

Smoking**				
Never	22462 (36.7)	726 (34.2)	74 (35.4)	0.092
Former	22144 (36.2)	822 (38.8)	82 (39.2)	
Current	16585 (27.1)	573 (27)	53 (25.4)	
Alcohol consumption**				
Yes	6699 (11.7)	201 (10.2)	21 (10.3)	0.104
No	50755 (88.3)	1778 (89.8)	182 (89.7)	
Physical activity**				
Low	14204 (25.2)	527 (26.8)	55 (28.1)	0.001
Medium	32316 (57.3)	1122 (57)	127 (64.8)	
High	9842 (17.5)	318 (16.2)	14 (7.1)	
Breast cancer in mother**				
Yes	3556 (6.3)	200 (10.4)	18 (9.4)	<0.001
No	53115 (93.7)	1728 (89.6)	173 (90.6)	
Breast cancer in sister**				
Yes	2250 (4.8)	109 (6.9)	13 (8.5)	<0.001
No	44798 (95.2)	1466 (93.1)	140 (91.5)	

* Mean values in breast cancer cases and non-cases with standard deviation in the brackets

** Number of participants in breast cancer cases and non-cases with proportions in the brackets

3.3.Results of survival analysis

Table 3 shows the results from the univariable and multivariable Cox regression between breast cancer cases, HR+ and HR- breast cancer cases. The assumptions of proportional hazards were fulfilled for all models.

In the univariable analysis, women who had 3 or more children had a 26% decreased risk of breast cancer compared to women without children (HR= 0.74, 95% CI: 0.65-0.85). This association between the number of children and breast cancer was statistically significant at the 5% level. Even though women with 1 or 2 children also had an 11% reduced risk of breast cancer (HR= 0.89, 95% CI: 0.78-1.01) compared to nulliparous women, the association was not statistically significant.

The multivariable analysis showed that multiparous women had a 26% lower risk of breast cancer compared to the reference group. (HR= 0.74, 95% CI: 0.65-0.85). Moreover, women with one or two children also had a 12 % reduced risk of breast cancer which was not statistically significant at the 5% level (HR= 0.88, 95% CI: 0.78-1.01).

Likewise, the univariable model for HR+ breast cancer showed that multiparous women had a 34% lower risk of HR+ cancer compared to childless women (HR= 0.66, 95% CI: 0.57- 0.77). Moreover, women with 1 or 2 children had a 16% lower risk of HR+ breast cancer (HR= 0.84, 95% CI: 0.73 - 0.97) in comparison to the reference group.

The multivariable analysis of HR+ breast cancer showed similar results to the univariable analysis. Compared to nullipara women, women with multiple children had 34% lower risk (HR=0.66, 95% CI: 0.57-0.76) and women with one or two children had 16% decreased risk of HR+ breast cancer (HR=0.84, 95% CI: 0.72 - 0.96). Both the univariable and multivariable associations for HR+ breast cancer cases were statistically significant at a 5% level.

On the contrary, the univariable model for HR- breast cancer cases showed a 24% increased risk of HR- cases in women with multiple children compared to nulliparous women (HR=1.24, 95% CI: 0.71-2.19). Compared to the reference group, women with 1 or 2 children had a 28% higher risk of HR- tumors (HR=1.28, 95% CI: 0.74 - 2.24).

Moreover, the multivariable analysis comparing with the reference group showed a greater risk of HR- breast cancer by 24% among women having multiple children (HR=1.24, 95% CI: 0.70 - 2.17). Women with fewer children had a 25 % greater risk of HR- breast cancer compared to nullipara women (HR=1.25, 95% CI: 0.72 -2.19). The results of the univariable and multivariable analysis for HR- cases were not statistically significant at the 5% level.

Table 3. Hazard ratios with 95% confidence intervals for breast cancer cases, HR+ cases and HR- cases according to the number of children in the Norwegian Women and Cancer Study (1991-2018)

	Breast cancer		HR+ breast cancer		HR- breast cancer	
Number of children	**Age-adjusted HR[1] (95% CI)**	**Multivariable HR[2] (95% CI)**	**Age-adjusted HR[1] (95% CI)**	**Multivariable HR[2] (95% CI)**	**Age-adjusted HR[1] (95% CI)**	**Multivariable HR[2] (95% CI)**
No child[3]	1	1	1	1	1	1
1-2 Children	0.89 (0.78-1.01)	0.88 (0.78-1.01)	0.84 (0.73-0.97)	0.84 (0.72-0.96)	1.28 (0.74-2.24)	1.25 (0.72-2.19)
3 or more children	0.74 (0.65-0.85)	0.74 (0.65-0.85)	0.66 (0.57-0.77)	0.66 (0.57-0.76)	1.24 (0.71-2.19)	1.24 (0.70-2.17)

[1] Univariable analysis

[2] Multivariable analysis including age, height, age at menarche and use of oral contraceptive

[3] Reference category

4. Discussion

4.1. Main results

The main aim of this study was to determine the effect of the number of children on the risk of HR+ breast cancer compared to HR- breast cancer using a prospective study design. This study showed a protective effect of the number of children on the risk of hormone receptor-positive and overall breast cancer. On the contrary, there was no similar protective effect of parity on hormone receptor-negative breast cancer risk. Rather, the results suggest that the risk of HR- breast cancer might be increased with the increasing number of children.

4.2.Comparison with previous studies

Looking at the literature on parity and breast cancer diagnosis, studies have shown consistent results with our findings. Steponavičienė, et.al (2020) found a decrease in the risk of breast cancer among parous Lithuanian women and the risk seems to be lower with the increase in the number of children (46). Jeong, S. H. et.al (2017) concluded that postmenopausal Korean women who gave birth to two or more children have a reduced risk of breast cancer and the risk decreases with the number of births (24).

A review paper by Anderson et al. involving twenty-two case-control and cohort studies on parity and HR+ and HR- breast cancer has shown similar results as our study. The authors stated that even though having children has a significant inverse association with HR+ cancer cases, many studies included in this review paper show no association with HR- tumors (47).

Likewise, the pooled analysis done by M. M. Gaudet et al. has consistent results with this thesis. The study pooled data from nine cohort studies concluded that the protective significant effect of parity is only in HR+ breast cancer while parity increases the risk of HR- breast cancer by 23% (48).

L. Bernstein et al. did a meta-analysis on the same topic including individual studies from 1995 to 2005 which is consistent with our findings. Based on this study, there is an inverse association between the number of children and ER+PR+ breast tumors whereas there is no effect of parity on ER-PR- tumors (49).

Another recently conducted meta-analysis by C. Li et al. involved studies between 2007 to 2021. In this meta-analysis, the researchers define TNBC as negative in estrogen, progesterone and HER2 receptors while luminal A cancers are positive in all three receptors. Since their definition of luminal A and TNBC are similar to the definitions of HR- and HR+ breast cancer in this master thesis, we have compared this study with our findings. The study shows the protective effect of parity is limited to only luminal A breast cancer. The combined effect estimate shows no association between parity and TNBC (50).

A study done in The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort on postmenopausal women showed somewhat different results in both univariable and multivariable hazard ratios. The study found that having multiple children has a protective effect on both subtypes of breast cancer (19). This difference from our study could be because we had a small number of HR- cases. Also in the EPIC cohort, the univariable model was adjusted for both age and center and the multivariable model was adjusted for many lifestyle and reproductive risk factors.

We have compared our findings with the African American Breast Cancer Epidemiology and Risk (AMBER) Consortium study as previous literatures showed inconsistent results in terms of HR- tumors. This cohort of African American women is the largest study to date on this topic and has a large sample of HR- breast cancer cases. Since African women are at higher risk of HR- tumors, this study provides strong evidence of the association between parity and HR- breast cancer. The authors concluded that parity is significantly associated with a thirty-three percent increase in the risk of TNBC/HR- breast cancer (51).

As multiple previous studies have shown that having children reduces the risk of HR+ breast cancer, we now focus on the possible reasons behind it. The estrogen and progesterone hormones play a crucial role as the hormonal changes influence the risk of cancer. The number of hormone receptors and exposure to both estrogen and progesterone can affect the breast. Previous papers have estimated that pregnancy can reduce the level of both female sex hormones in the blood plasma (49).

Having multiple births also increases globulin levels which help to limit exposure to both hormones. As mentioned in the introduction part, having children also changes the breast tissues which reduces the influence of both estrogen and progesterone hormones. Another reason could be that only estrogen receptor-positive carcinoma has a diverse expression in immune and inflammatory pathways which is called parity-related gene signature (49).

4.3.Strengths of the study

The main strength of this thesis was the use of a prospective cohort study design to answer the research question. Among the epidemiological studies, cohort study helps to determine the incidence rates as it involves follow-up of participants. Moreover, this study design can be used to make causal inferences as the exposure was measured before the occurrence of the outcome (52). The NOWAC study's participants represent women in Norway who have been followed for a long period of twenty-seven years. Since cancer is one of the diseases that take years to develop, this long follow-up helped to determine the correct risk estimation (53).

Even though the number of children was self-reported by participants, the external validity of NOWAC showed no difference in parity between the participants within this cohort and non-participants(54). The outcome data for breast cancer cases were drawn from CRN. This registry had a 98.8% data completeness and has been recording data on cancer patients from laboratories and hospitals since 1952 (55).

In the final regression model, many studies do not give any reason for selecting some variables as confounders, making it difficult to interpret the associations (56). One of the major strengths of this study was the use of DAG in the selection of covariates with strong reasoning on how each variable was related to the exposure and the outcome.

4.4.Weakness of the study

The main drawback of this study was a small number of HR- breast cancer cases compared to HR+ cancer cases which can be explained by the following reasons. Only a small proportion of breast cancer cases are of the HR- cancer subtype, among the total breast cancer cases diagnosed worldwide (50). Previous research has also shown higher rates of HR+ breast cancer in European women whereas African women are frequently diagnosed with HR- breast cancer (51, 57). Moreover, the breast cancer trends in the western world from the 1990s up until 2015 showed a lower incidence of HR- tumors (58, 59). The analysis limited to only postmenopausal women also reduced the number of HR- cases among the total breast cancer cases diagnosed in Norway.

As this master thesis focused on complete case analysis, we removed all missing values in the covariates. Multiple imputations could have been used to address the missing values, but this would be beyond the scope of a master's thesis. All the lifestyle and reproductive variables in the NOWAC cohort were self-reported which could lead to information bias. However, the information was collected before the occurrence of cancer, so the misclassification was most likely to have been non-differential. As the consequence, the observed relative risk estimates were likely to be somewhat attenuated.

Although this study included many variables which are risk factors for breast cancer, data on maternal age at birth of the first child was not used in the thesis. A combined variable of both the number of children and the mother's age at first birth could be used as the exposure to estimate the risk of breast cancer subtypes but it would make this master thesis lengthy and broad. However, another study can be suggested for further analysis on this topic.

Furthermore, within the multivariable survival analysis, the lifestyle variables such as their weight, smoking habits, physical activity, and alcohol consumption were not adjusted for. Information on the number of children they have, and all questionnaire variables was collected at the same time using a questionnaire. There was no available information about the participant's lifestyle activities in their teen years which made it difficult to determine if started smoking or drinking and were physically inactive or overweight before or after their pregnancy. Since we assumed these variables were more likely to be mediators, they were not adjusted for in the survival model.

5. Conclusion

In conclusion, having children was associated with a lower risk of breast cancer overall and hormone receptor-positive breast cancer diagnosis in Norwegian women. On the contrary, we have not observed the same association between the number of children and the risk of hormone receptor-negative breast cancer.

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