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Breast cancer risk factors and survival by tumor subtype: pooled analyses from the Breast Cancer Association Consortium

A full list of authors and affiliations appears at the end of the article.

Abstract

Background: It is not known if modifiable lifestyle factors that predict survival after invasive breast cancer differ by subtype.

Methods: We analyzed data for 121 435 women diagnosed with breast cancer from 67 studies in the Breast Cancer Association Consortium with 16 890 deaths (8554 breast cancer-specific) over 10 years. Cox regression was used to estimate associations between risk factors and 10-year all-cause mortality and breast cancer-specific mortality overall, by estrogen receptor (ER) status, and by intrinsic-like subtype.

Results: There was no evidence of heterogeneous associations between risk factors and mortality by subtype (adjusted p>0.30). The strongest associations were between all-cause mortality and BMI ≥30 *vs* 18.5–25 kg/m^2 (HR (95%CI): 1.19 (1.06,1.34)); current *vs* never smoking (1.37 (1.27,1.47)), high *vs* low physical activity (0.43 (0.21,0.86)), age ≥30 years *vs* <20 years at first pregnancy (0.79 (0.72,0.86)); >0 to <5 years *vs* ≥10 years since last full term birth (1.31 (1.11,1.55)); ever *vs* never use of oral contraceptives (0.91 (0.87,0.96)); ever vs never use of menopausal hormone therapy, including current estrogen-progestin therapy (0.61 (0.54,0.69)). Similar associations with breast cancer mortality were weaker; e.g. 1.11 (1.02,1.21) for current *vs* never smoking.

Conclusions: We confirm associations between modifiable lifestyle factors and 10-year all-cause mortality. There was no strong evidence that associations differed by ER status or intrinsic-like subtype.

Impact: Given the large dataset and lack of evidence that associations between modifiable risk factors and 10-year mortality differed by subtype, these associations could be cautiously used in prognostication models to inform patient-centered care.

Keywords

breast cancer; survival; intrinsic-like subtypes; risk factors; mortality

Corresponding author: Marjanka K. Schmidt, Netherlands Cancer Institute, Amsterdam, 1066 CX, The Netherlands. Phone: +31 20 512 2767, mk.schmidt@nki.nl.

†Shared first authors,

#Shared last authors

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Introduction

Breast cancer is a heterogeneous disease with differing risk factors (1) and etiologies (2), and correspondingly differential response to treatment (3) as well as prognosis (4). Despite the heterogeneous nature of breast cancer, there are few studies investigating possible differential relationships between risk factors and mortality according to tumor subtypes. Given that more women are surviving after a breast cancer diagnosis (5), identifying lifestyle and personal factors associated with mortality after breast cancer according to tumor subtypes is important.

A recent systematic literature review and meta-analysis in breast cancer patients (6) concluded that there was limited suggestive evidence for physical activity, foods containing fiber, and foods containing soy being associated with decreased all-cause mortality, and for body fatness, weight gain, and intake of total fat and saturated fatty acids being associated with increased all-cause mortality. However, there was a lack of consistent data to draw conclusions for other dietary and nutritional risk factors regarding all-cause mortality or breast cancer-specific mortality, either overall or by molecular subtype (6).

In a large population-based prospective cohort, cigarette smoking was found to be related to higher mortality from both breast cancer and smoking related diseases (7). Findings regarding reproductive factors have however been conflicting. Most studies have found no association between mortality after breast cancer and age at menarche (8–11), parity (10,12–14), history of breastfeeding (11), duration of breastfeeding (11,14), history of oral contraceptive use (10,11,15,16), or duration of oral contraceptive use (11,15–17). There are some reports of decreased mortality associated with younger age at menarche (18,19), parity (20), history of breastfeeding (12,21,22), longer duration of breastfeeding (12), and menopausal hormone therapy (MHT) (23,24). Other studies have reported increased mortality associated with younger age at menarche (25), parity, particularly among women with luminal breast cancers (26) and women diagnosed before age 50 (13,27), shorter time interval since last birth (8,10,11,14,26–30), and MHT use, particularly combined estrogen-progestin (31–33). There is paucity of data and no clear evidence for differential effects of the investigated risk factors with mortality for different intrinsic-like subtypes. A more detailed investigation is essential to improve our understanding of these relationships. Therefore, we aimed to investigate associations between prediagnosis reproductive and lifestyle risk factors on 10-year all-cause and breast cancer-specific mortality by tumor subtype of breast cancer patients. We also investigated whether prognostic models could be improved by inclusion of these factors.

Methods

Study population and exposure assessment

We employed data from studies participating in the Breast Cancer Association Consortium (BCAC), which are described in Supplementary Table S1. Details of the inclusion criteria are presented in the Supplementary Methods. The final study population consisted of 121 435 invasive, stage I-III, female breast cancer patients from 67 studies participating in the BCAC. All individual studies were approved by their appropriate institutional review boards

and/or medical ethical committees. Written informed consent was obtained from all study subjects.

We focused on 15 breast cancer lifestyle and reproductive risk factors: age at menarche, parity, age at first full-term pregnancy (FFTP), time since last full term birth, ever breastfeeding, duration of breastfeeding, body mass index (BMI) (investigated both overall and separately within postmenopausal and pre/perimenopausal women), adult height, oral contraceptives (OC) use, menopausal hormone therapy (MHT) use, smoking status, pack-years of smoking, recent alcohol consumption, cumulative alcohol consumption, and physical activity. Exposure information was collected pre-diagnosis in nested case-control/prospective cohort studies and at or shortly after diagnosis in case-control studies and patient cohorts. Time since last full-term birth was calculated as the time interval between age at diagnosis and age at last full-term birth. Women were defined as postmenopausal if the last menstruation occurred >12 months before diagnosis, and as pre/perimenopausal otherwise. Menopausal status and MHT use were combined into a single variable with 8 categories, where former use was use more than 6 months prior to diagnosis and current use was use at date of diagnosis or within 6 months prior to date of diagnosis. Ever use of OC was defined as use for ≥4 months and never use as <4 four months of use. There were 3 categories for smoking status: never, former and current, with current defined as smoking in the last year before diagnosis. A pack-year constituted 20 cigarettes smoked per day for one year. Alcohol consumption and physical activity were based on the last year before diagnosis. For comparison with other studies, tertiles of physical activity (hours/week) were used. Cumulative alcohol consumption was that consumed over a lifetime until the date of diagnosis.

Breast cancer intrinsic-like subtypes

The source of tumor marker data (i.e., data on expression of ER, PR, HER2, and grade) and assessment of specific tumor markers varied across the studies and included clinical/pathology records and immunohistochemistry (IHC) staining of whole tumor sections or tissue microarrays (34). Breast tumors were classified according to estrogen receptor (ER) status (positive versus negative) and according to intrinsic-like subtypes based on ER, progesterone receptor (PR), the human epidermal growth factor receptor 2 (HER2), and grade (35).

Outcome assessment

Vital status was ascertained by individual studies. Cause of death was coded according to the 10^{th} revision of the International Classification of Diseases (ICD-10-WHO). The primary study outcomes were 10-year all-cause mortality (death from any cause) and 10-year breast cancer-specific mortality (death from breast cancer; coded as ICD-10-C50).

Statistical analyses

Multiple imputation of missing data—Multiple imputation, performed using R package MICE (version 3.2.0), was used to handle missing values of both risk factor and clinical-pathological variables as described in the Supplementary Methods. A list of imputed

variables and corresponding percentages of missing values is provided in Supplementary Table S2.

Associations of individual and multiple risk factors with all-cause and breast cancer-specific mortality overall and by subtype—Delayed-entry Cox regression models were used to assess associations between lifestyle and reproductive breast cancer risk factors and 10-year all-cause and breast cancer mortality in all patients and by tumor subtypes according to ER status and intrinsic-like subtypes. Time-to-event started from date of diagnosis, and time-at-risk started from date of recruitment into the study if it was after date of diagnosis. Age of the patient was used as the time-scale so that patient age is implicitly accounted for without the need to estimate its coefficient (36). For breast cancer-specific mortality, women who died within 10 years from diagnosis and whose cause of death was not breast cancer (24.6% of the total number of deaths) or was unknown (24.8% of the total number of deaths) were censored at age of death. Women who died 10 years or more after diagnosis were censored at their age at 10 years after diagnosis. Women who did not experience the event of interest (death from any cause or death from breast cancer) within the first 10 years following diagnosis were censored at their age at last follow-up. All models were stratified by study and adjusted for tumor size, nodal status, tumor grade (except for luminal-B-HER2-negative-like), and systemic treatment (adjuvant endocrine therapy (yes/no), (neo)adjuvant chemotherapy (yes/no) and trastuzumab (yes/no)). Cox models were performed for each risk factor individually using imputed data, and as sensitivity analyses using complete-case data (Supplementary Table S3 and S4; Supplementary Figure S1–S16). Multiple testing was accounted for using the Benjamini-Hochberg method, as described in the Supplementary Methods. Additional sensitivity analyses based on prospective studies only were performed in order to address potential recall bias.

Potential heterogeneity of the association estimates across tumor subtype was tested by means of a likelihood ratio test comparing models with and without an interaction term between the variable representing a specific risk factor and the variable representing the subtype (based on ER status only or according to the intrinsic-like classification).

To account for the interplay between risk factors, we fitted a single multivariable Cox regression model including all risk factors of interest (with the exception of pack-years) to assess associations with 10-year all-cause and breast cancer-specific mortality. Similar to analyses of individual risk factors with outcomes, the Cox model was stratified by study and adjusted for covariates as above. Since this analysis was performed in all patients, ER, PR and HER2 status were included as additional covariates.

The proportional hazards assumption was assessed for each risk factor of interest, based on all included cases, after applying exclusion criteria for individual subjects (not imputed). Plots of the Schoenfeld residuals did not show strong evidence of deviation from the proportional hazard assumption.

Time-dependent ROC curve analyses were performed, as described in the Supplementary Methods, to assess whether the additional inclusion of the risk factors investigated would

add discriminative power compared to a prognostic model based only on the established breast cancer prognostic factors.

Results

There were 16 890 deaths overall and 8554 breast cancer deaths after a follow-up time of 10 years in 121 435 breast cancer patients (Table 1). The median follow-up time for patients included in the study was 7.7 years. Overall median age at diagnosis was 57 years (IQR 48–65). Distribution of tumor and treatment characteristics and risk factors in all patients and by subtype is shown in Table 1.

Associations of individual risk factors with all-cause and breast cancer-specific mortality overall and by subtype

Associations of individual risk factors with all-cause mortality are shown in Table 2. Parous women had lower mortality compared to nulliparous, with strongest associations observed in women who had 1 (HR (95%CI): 0.87 (0.79, 0.96)) or 2 full-term pregnancies HR (95%CI): 0.86 (0.77, 0. 96). Among parous women, lower all-cause mortality was associated with later age at FFTP (P=1.0E-15), with HR of 0.79 (95%CI: (0.73, 0.86)) for women with FFTP at age ≥30 years compared to <20 years. Higher all-cause mortality was associated with a more recent full-term pregnancy only in women with ER+ tumors (time since last full-term birth 0–5 years versus ≥10 years HR (95%CI): 1.36 (1.12, 1.65)), but there was no statistical heterogeneity by ER status (P=8.5E-01; Table 3).

In both pre- and postmenopausal women, higher BMI was associated with higher all-cause mortality. The evidence was stronger for postmenopausal women with HR of 1.20 (95%CI: 1.12, 1.29) for obese (≥30 kg/m^2) women compared to normal weight women (BMI 18.5–25 kg/m^2). Low BMI was likewise associated with higher all-cause mortality (HR 1.53 (95%CI: 1.30, 1.80) for underweight (BMI < 18.5 kg/m^2) compared to normal weight.

Exogenous hormone exposure was associated with reduced all-cause mortality. Compared to never use, ever OC use was associated with decreased all-cause mortality (HR (95%CI): 0.88 (0.84, 0.93), P=1.6E-04). Overall, use of MHT was also associated with decreased risk of all-cause mortality, with the strongest association for current users of combined estrogen and progesterone therapy compared to never users (HR (95%CI): 0.58 (0.52, 0.65)).

Current cigarette smoking compared to never smoking was associated with higher all-cause mortality (HR (95%CI): 1.38 (1.30, 1.45)). A 10-unit increase in the number of pack-years smoked was also associated with an increased risk of all-cause mortality (HR (95%CI): 1.11 (1.06, 1.15), P=1.2E-03). Physical activity was associated with decreased all-cause mortality (HR (95%CI): 0.42 (0.21, 0.85) for highest vs lowest tertile.

There was no evidence of heterogeneity by ER status or by intrinsic-like subtype (Table 2 and Table 3). Some variability was observed in estimates for women who had a recent full-term birth, especially comparing those 0–5 years to ≥10 years where HRs (95%CI) ranged from 1.55 (1.08, 2.24) for luminal A-like tumors to 0.93 (0.68, 1.27) for triple negative (TN) tumors, although there was no overall evidence of heterogeneity (P=1.00E+00).

Results of associations between single risk factors and breast cancer-specific mortality were generally in line with those observed for all-cause mortality but weaker (Table 4). The exception was time since last full-term birth, where the association with breast cancer-specific mortality appeared to be somewhat stronger than with all-cause mortality, especially for the ER-positive (P=2.2E-04) and luminal A-like subtypes (P=5.5E-03). There was also some variability in the association estimates related to time since last full-term birth according to ER status and intrinsic-like subtype, notably for last full-term birth 0–5 years versus ≥10 years prior to diagnosis for luminal A-like (HR (95%CI): 1.79 (1.27, 2.51)) compared to that for TN (HR (95%CI): 0.90 (0.65, 1.24)). Risk factors associated with all-cause mortality, such as parity, OC use, BMI in postmenopausal women, smoking, and physical activity were not associated with breast cancer-specific mortality after multiple testing correction.

Sensitivity analyses relating to associations between individual risk factors with outcomes restricted to the complete-case data yielded results that were generally consistent with those from the imputed data analyses for both all-cause and breast cancer-specific mortality, as point estimates were mostly in the same direction and the corresponding confidence intervals were largely overlapping (Supplementary Figures S1–S16). For physical activity, the association with all-cause mortality was attenuated, particularly in the analyses based on all patients (HR (95%CI): 0.82 (0.62, 1.12); Supplementary Table S3).

Sensitivity analyses based on prospective studies only yielded results that were generally in line with those from analyses based on all studies though confidence intervals were wider due to decreased numbers in the dataset (Supplementary Figures S17–S22)).

Associations of multiple risk factors with all-cause and breast cancer-specific mortality overall

Accounting for all risk factors simultaneously in the Cox model did not substantially change HRs for most risk factors (Table 5). Of the three individually-associated reproductive variables, parity was no longer associated with all-cause mortality after adjusting for age at FFTP and time since last full-term birth. Similar to results from individual risk factors and all-cause mortality, current use of combined estrogen-progestin compared to never MHT use (HR (95%): 0.61 (0.54, 0.69)) and ever use of OC compared to never OC use (HR (95%): 0.91 (0.87, 0.96) were both still associated with all-cause mortality. All-cause mortality was increased in current smokers compared to non-smokers (HR (95%CI): 1.37 (1.27, 1.47). At least 5.5 hours/week of physical activity decreased risk of all-cause mortality (HR (95%CI): 0.43 (0.21, 0.86)) (highest *vs* lowest tertile)).

Associations of multiple risk factors with breast cancer-specific mortality (Table 6) also remained substantially unchanged compared to individual risk factors associations except for parity (Table 4).

Sensitivity analyses relating to associations of multiple risk factors with outcomes restricted to the complete-case data yielded results that were mostly consistent with those of the imputed data, with two exceptions (Supplementary Tables S7 and S8; Supplementary Figures S23 and S24). Former versus never smoking was associated with increased all-cause

mortality (HR (95%CI: 1.69 (1.16, 2.47) and breast cancer-specific mortality (HR (95%CI: 1.71 (1.07, 2.73) in the complete-case analysis, in contrast to the imputed data analysis (HR (95%CI): 1.03 (0.98, 1.07) and HR (95%CI): 0.94 (0.88, 1.01), respectively). On the other hand, physical activity was no longer associated with all-cause mortality in the complete-case analysis.

Evaluation of the discriminative power of the models

Supplementary Figure S25 and Supplementary Figure S26 show the area under the curve values over a range of ages for a Cox model only including classical prognostic factors (i.e. tumor characteristics and treatment) and for a Cox model additionally including the risk factors investigated. We observed a decrease in discriminative power of both models with older ages. The discriminative power of the model including additional risk factors was higher over all ages compared to that based on only classical prognostic factors. For all-cause mortality the concordance index increased from 0.69 to 0.71 when adding risk factors to the model (Supplementary Figure S25). For breast cancer-specific mortality, the concordance index was 0.74 for both models (Supplementary Figure S26).

Discussion

Breast cancer risk factors for mortality after a breast cancer diagnosis according to tumor subtype have not been established. Identification and characterization of these associations is important since they may be useful for prognostication at the time of diagnosis. Therefore, our main objectives were to quantify associations between breast cancer risk factors and all-cause and breast cancer-specific mortality and to evaluate whether associations differ by tumor subtype. We found evidence for associations between modifiable lifestyle risk factors and all-cause mortality, namely, obesity, smoking, and physical activity as well as associations with reproductive risk factors, age at FFTP, and time since last birth, and exogenous hormone use in the form of OCs and MHTs. Similar associations were also found with breast cancer-specific mortality. After correction for multiple testing, there was no evidence for differential associations by ER status or intrinsic-like subtype.

Data on breast cancer risk factors in relation to survival according to tumor subtypes are scarce with a few studies reporting possibly differential associations between survival and older age at menarche (18,37), breastfeeding (22), parity (26,37), older age at FFTP (37), recent last birth (26), and low (37) and high BMI (37,38) by tumor subtypes, and other studies reporting no differential associations with MHT use (39–41). Our data do not support the previous reports, which might have been chance findings.

Our findings indicate that several modifiable risk factors are associated with survival. Low and high BMI (8,10,12,37) as well as smoking (7,42) were found to increase both all-cause and breast cancer-specific mortality, while physical activity was found to decrease all-cause mortality (43) with similar patterns of association for breast cancer-specific mortality (6). The observed associations with high BMI could, in part, be due to obese breast cancer survivors being less responsive to aromatase inhibitor treatments (8,44) or chemotherapy (8,45,46). A systematic review and meta-analysis also highlights evidence for a non-linear *J*-shaped dose-response relationship between BMI and mortality (47), consistent with findings

from the current analysis that underweight women may also be at increased risk of mortality compared to normal weight women. The attenuated association between smoking and breast cancer-specific mortality compared to overall mortality could be attributed to the association of smoking with diseases other than breast cancer such as lung cancer and cardiovascular diseases. Comparable to results from two meta-analyses (6,43), we found high physical activity to be associated with lower risk of all-cause mortality with similar patterns for breast cancer-specific mortality. Body weight, smoking, and physical activity are relevant breast cancer risk factors in that reduction in weight and smoking, as well as the promotion of physical activity are practical and useful targets for both patients and public health. The relevance of obesity and physical activity as modifiable factors is strengthened by growing evidence that postdiagnosis weight gain increases mortality in addition to prediagnosis BMI (6,48) and changes in pre- to postdiagnosis physical activity are also associated with mortality (6,49).

In line with previous literature, associations with age at menarche, number of full-term pregnancies, and breastfeeding with mortality were null after accounting for other reproductive variables (8,10–12). Our data substantiate previously suggested patterns of association where risk of mortality decreases with older age at FFTP (8,10,11,37) and a more recent last birth increases mortality, particularly breast cancer-specific mortality (8,13,18,28–30). The reasons for these associations are unclear. Women of higher socio-economic status often have their first child later and have better access to health care, lifestyle and nutrition, all of which can decrease mortality. The association of a more recent last birth with increased breast cancer-specific mortality appeared to be differential by ER status and intrinsic-like subtype, although not after accounting for multiple testing corrections. Two previous studies also found such associations only for luminal tumors (26,29). Breast tumors occurring during pregnancy, post-partum, or during lactation can be subject to treatment and diagnosis delays, both of which may result in poorer prognosis.

Exposure to exogenous hormones – OC and MHT – was observed to be associated with decreased mortality irrespective of tumor subtype. Decreased all-cause mortality with ever OC use has been inconsistently reported (8,10,15,16) and may be due to differences in timing, duration, and dose of OCs. Ever MHT use was associated with decreased all-cause and breast cancer-specific mortality and corroborate the results from published meta-analyses (23,24). On the other hand, current MHT use, particularly combined estrogen-progestin, has been found to be associated with increased breast cancer-specific mortality in population-based prospective cohort studies (32,33), but this estimate combines the joint effects of incidence and case-fatality. Unmeasured factors related to MHT such as differences in “health-seeking behavior” and medical surveillance might be present, as women can only receive exogenous hormones after consultation with a physician, which could not be accounted for in this analysis, so that residual confounding cannot be excluded. Thus the observed association between MHT and survival does not imply that MHT use after diagnosis would be beneficial for survival, especially since it is well-established that MHT use increases risk of breast cancer (50).

A major strength of our study is the sample size, making it the largest dataset of breast cancer patients available to date. Due to the large sample size, we were able to assess

associations by ER and intrinsic-like subtype as well as heterogeneity between subtypes. We have collected and harmonized information on numerous potential risk factors and have fitted multivariable models that simultaneously accounted for established prognostic factors as well as first-line cancer treatment.

Despite centralized data harmonization, residual heterogeneity in the studies with varying designs and different coding of variables may still be present and affect our results. Timing of exposure information collection with respect to diagnosis also differs between study designs. Whereas prediagnosis information is generally collected prospectively in nested case-control/prospective cohort studies and retrospectively in case-control studies, patient cohort studies are more likely to collect postdiagnosis information. While some types of risk factor information such as current MHT use may be affected by whether they are assessed before or after diagnosis, this is less likely to be the case for most risk factors we considered, such as reproductive history, and BMI. In the current analysis, nine cohort studies provided risk factor information collected more than one year before diagnosis, comprising 11.4% of the total analyzed sample. Their inclusion is not likely to have substantially affected our evaluation of associations between risk factors and survival also by tumor subtype. Delays in patient recruitment can lead to survival bias that we accounted for using delayed entry in the regression models, which if well-specified, should provide unbiased estimates (8). An additional limitation was the fact that some studies did not completely report cause of death. In particular, for 24.8% of the total number of deaths it was unknown whether they were due to breast cancer or to other causes. This could have led to a loss of power in the breast cancer-specific analyses, if most of the deaths of unknown cause were actually due to breast cancer. Another challenge was the large proportion of missing values for some of the variables under study, particularly alcohol consumption and physical activity. We included these variables in our study to provide a comprehensive analysis of all the potentially relevant risk factors for survival. We addressed the missing data issue by employing multiple imputation, which allowed us to keep the sample size intact and, if data are missing at random, should provide unbiased estimates for the associations of interest. A recent simulation study showed that this is the case even for large proportions of missing values, up to 90%, provided that imputation models are correctly specified, therefore concluding that the proportion of missing values itself should not be used to determine whether to perform multiple imputation (51).

Sensitivity analysis using complete-case data confirmed that for most variables, the results were consistent with imputed results, with the exception of former smoking and physical activity. Former smoking was associated with both all-cause and breast cancer-specific mortality when only complete-case data was used, while physical activity was not associated with mortality in the complete-case analysis. For physical activity, our results based on multiple imputed data were consistent with those from a recent systematic review and meta-analysis where the summary HR (95%CI) for prediagnosis physical activity and all-cause mortality was 0.82 (0.76–0.87) and for postdiagnosis physical activity and all-cause mortality was 0.58 (0.52–0.65) (43). Former smoking was not associated with 10-year mortality based on the analysis of imputed data, which has also been reported previously (8).

While we have been able to investigate associations between numerous pertinent breast cancer risk factors with mortality, we were unable to consider others such as mode of detection and comorbidities, which may be relevant for mortality. Socioeconomic status (SES) could also be a potential confounder in the associations between some of the considered risk factors and mortality. Risk factors that would be most strongly associated with SES include age at first full-term pregnancy, as mentioned previously, as well as exogenous hormone use (OC and MHT) which might be less accessible to women with lower SES. Some studies that have accounted for SES have still found reduced case fatality in current users of MHT (39,41), so SES seems unlikely to fully explain the association between MHT use and breast cancer survival.

In conclusion, we provide evidence that associations of breast cancer risk factors with survival after a diagnosis of breast cancer do not substantially differ by tumor subtype. The absence of effect heterogeneity by subtype suggests that the associated risk factors may be generalizable to all tumors, which facilitates their use in prognostication models and public health strategies without the need for subtype-specific considerations.

Supplementary Material

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Authors

Anna Morra[1,†], Audrey Y. Jung[2,†], Sabine Behrens[2], Renske Keeman[1], Thomas U. Ahearn[3], Hoda Anton-Culver[4], Volker Arndt[5], Annelie Augustinsson[6], Päivi K. Auvinen[7,8,9], Laura E. Beane Freeman[3], Heiko Becher[10,11], Matthias W. Beckmann[12], Carl Blomqvist[13,14], Stig E. Bojesen[15,16,17], Manjeet K. Bolla[18], Hermann Brenner[5,19,20], Ignacio Briceno[21], Sara Y. Brucker[22], Nicola J. Camp[23], Daniele Campa[2,24], Federico Canzian[25], Jose E. Castelao[26], Stephen J. Chanock[3], Ji-Yeob Choi[27,28], Christine L. Clarke[29], for the ABCTB Investigators, Fergus J. Couch[30], Angela Cox[31], Simon S. Cross[32], Kamila Czene[33], Thilo Dörk[34], Alison M. Dunning[35], Miriam Dwek[36], Douglas F. Easton[18,35], Diana M. Eccles[37], Kathleen M. Egan[38], D. Gareth Evans[39,40], Peter A. Fasching[12,41], Henrik Flyger[42], Manuela Gago-Dominguez[43,44], Susan M. Gapstur[45], José A. García-Sáenz[46], Mia M. Gaudet[45], Graham G. Giles[47,48,49], Mervi Grip[50], Pascal Guénel[51], Christopher A. Haiman[52], Niclas Håkansson[53], Per Hall[33,54], Ute Hamann[55], Sileny N. Han[56], Steven N. Hart[57], Mikael Hartman[58,59], Jane S Heyworth[60], Reiner Hoppe[61,62], John L. Hopper[48], David J. Hunter[63,64], Hidemi Ito[65,66], Agnes Jager[67], Milena Jakimovska[68], Anna Jakubowska[69,70], Wolfgang Janni[71], Rudolf Kaaks[2], Daehee Kang[27,28,72], Pooja Middha Kapoor[2,73], Cari M. Kitahara[74], Stella Koutros[3], Peter Kraft[64,75], Vessela N. Kristensen[76,77], for the NBCS Collaborators, James V. Lacey[78,79], Diether Lambrechts[80,81], Loic Le Marchand[82], Jingmei Li[83], Annika Lindblom[84,85], Jan Lubiński[69], Michael Lush[18], Arto Mannermaa[7,86,87], Mehdi Manoochehri[55], Sara Margolin[54,88], Shivaani Mariapun[89,90], Keitaro Matsuo[65,66], Dimitrios Mavroudis[91], Roger L. Milne[47,48,49], Taru A. Muranen[92], William G. Newman[39,40], Dong-Young Noh[93], Børge G. Nordestgaard[15,16,17], Nadia Obi[94],

Andrew F. Olshan[95], Håkan Olsson[6], Tjoung-Won Park-Simon[34], Christos Petridis[96], Paul D.P. Pharoah[18,35], Dijana Plaseska-Karanfilska[68], Nadege Presneau[36], Muhammad U. Rashid[55,97], Gad Rennert[98], Hedy S. Rennert[98], Valerie Rhenius[35], Atocha Romero[99], Emmanouil Saloustros[100], Elinor J. Sawyer[101], Andreas Schneeweiss[102,103], Lukas Schwentner[71], Christopher Scott[57], Mitul Shah[35], Chen-Yang Shen[104,105], Xiao-Ou Shu[106], Melissa C. Southey[47,49,107], Daniel O. Stram[52], Rulla M. Tamimi[64,108], William Tapper[37], Rob A.E.M. Tollenaar[109], Ian Tomlinson[110,111], Diana Torres[55,112], Melissa A. Troester[95], Thérèse Truong[51], Celine M. Vachon[113], Qin Wang[18], Sophia S. Wang[78,79], Justin A. Williams[23], Robert Winqvist[114,115], Alicja Wolk[53,116], Anna H. Wu[52], Keun-Young Yoo[117,118], Jyh-Cherng Yu[119], Wei Zheng[106], Argyrios Ziogas[4], Xiaohong R. Yang[3], A. Heather Eliassen[64,120], Michelle D. Holmes[64,120], Montserrat García-Closas[3], Soo Hwang Teo[121,122], Marjanka K. Schmidt[1,123,#], Jenny Chang-Claude[2,124,#]

Affiliations

[1]The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Division of Molecular Pathology, Amsterdam, The Netherlands. [2]German Cancer Research Center (DKFZ), Division of Cancer Epidemiology, Heidelberg, Germany. [3]National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Division of Cancer Epidemiology and Genetics, Bethesda, MD, USA. [4]University of California Irvine, Department of Epidemiology, Genetic Epidemiology Research Institute, Irvine, CA, USA. [5]German Cancer Research Center (DKFZ), Division of Clinical Epidemiology and Aging Research, Heidelberg, Germany. [6]Lund University, Department of Cancer Epidemiology, Clinical Sciences, Lund, Sweden. [7]University of Eastern Finland, Translational Cancer Research Area, Kuopio, Finland. [8]University of Eastern Finland, Institute of Clinical Medicine, Oncology, Kuopio, Finland. [9]Kuopio University Hospital, Department of Oncology, Cancer Center, Kuopio, Finland. [10]University Medical Center Hamburg-Eppendorf, Institute of Medical Biometry and Epidemiology, Hamburg, Germany. [11]Charité – Universitätsmedizin Berlin, Institute of Biometry and Clinical Epidemiology, Berlin, Germany. [12]University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Department of Gynecology and Obstetrics, Comprehensive Cancer Center ER-EMN, Erlangen, Germany. [13]University of Helsinki, Department of Oncology, Helsinki University Hospital, Helsinki, Finland. [14]Örebro University Hospital, Department of Oncology, Örebro, Sweden. [15]Copenhagen University Hospital, Copenhagen General Population Study, Herlev and Gentofte Hospital, Herlev, Denmark. [16]Copenhagen University Hospital, Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Herlev, Denmark. [17]University of Copenhagen, Faculty of Health and Medical Sciences, Copenhagen, Denmark. [18]University of Cambridge, Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, Cambridge, UK. [19]German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Division of Preventive Oncology, Heidelberg, Germany. [20]German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), Heidelberg, Germany. [21]Universidad de La Sabana, Medical Faculty, Bogota, Colombia. [22]University of Tübingen,

Department of Gynecology and Obstetrics, Tübingen, Germany. [23]University of Utah, Department of Internal Medicine and Huntsman Cancer Institute, Salt Lake City, UT, USA. [24]University of Pisa, Department of Biology, Pisa, Italy. [25]German Cancer Research Center (DKFZ), Genomic Epidemiology Group, Heidelberg, Germany. [26]Instituto de Investigacion Sanitaria Galicia Sur (IISGS), Xerencia de Xestion Integrada de Vigo-SERGAS, Oncology and Genetics Unit, Vigo, Spain. [27]Seoul National University Graduate School, Department of Biomedical Sciences, Seoul, Korea. [28]Seoul National University, Cancer Research Institute, Seoul, Korea. [29]University of Sydney, Westmead Institute for Medical Research, Sydney, New South Wales, Australia. [30]Mayo Clinic, Department of Laboratory Medicine and Pathology, Rochester, MN, USA. [31]University of Sheffield, Sheffield Institute for Nucleic Acids (SInFoNiA), Department of Oncology and Metabolism, Sheffield, UK. [32]University of Sheffield, Academic Unit of Pathology, Department of Neuroscience, Sheffield, UK. [33]Karolinska Institutet, Department of Medical Epidemiology and Biostatistics, Stockholm, Sweden. [34]Hannover Medical School, Gynaecology Research Unit, Hannover, Germany. [35]University of Cambridge, Centre for Cancer Genetic Epidemiology, Department of Oncology, Cambridge, UK. [36]University of Westminster, School of Life Sciences, London, UK. [37]University of Southampton, Faculty of Medicine, Southampton, UK. [38]Moffitt Cancer Center & Research Institute, Division of Population Sciences, Tampa, FL, USA. [39]University of Manchester, Manchester Academic Health Science Centre, Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, Manchester, UK. [40]St Mary's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, North West Genomics Laboratory Hub, Manchester Centre for Genomic Medicine, Manchester, UK. [41]University of California at Los Angeles, David Geffen School of Medicine, Department of Medicine Division of Hematology and Oncology, Los Angeles, CA, USA. [42]Copenhagen University Hospital, Department of Breast Surgery, Herlev and Gentofte Hospital, Herlev, Denmark. [43]Galician Public Foundation of Genomic Medicine (FPGMX), Genomic Medicine Group, International Cancer Genetics and Epidemiology Group, Health Research Institute of Santiago (IDIS), Santiago de Compostela, Spain. [44]University of California San Diego, Moores Cancer Center, La Jolla, CA, USA. [45]American Cancer Society, Behavioral and Epidemiology Research Group, Atlanta, GA, USA. [46]Instituto de Investigación Sanitaria San Carlos (IdISSC), Centro Investigación Biomédica en Red de Cáncer (CIBERONC), Medical Oncology Department, Hospital Clínico San Carlos, Madrid, Spain. [47]Cancer Council Victoria, Cancer Epidemiology Division, Melbourne, Victoria, Australia. [48]The University of Melbourne, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Melbourne, Victoria, Australia. [49]Monash University, Precision Medicine, School of Clinical Sciences at Monash Health, Clayton, Victoria, Australia. [50]University of Oulu, Department of Surgery, Oulu University Hospital, Oulu, Finland. [51]INSERM, University Paris-Saclay, Center for Research in Epidemiology and Population Health (CESP), Team Exposome and Heredity, Villejuif, France. [52]University of Southern California, Department of Preventive

Medicine, Keck School of Medicine, Los Angeles, CA, USA. [53]Karolinska Institutet, Institute of Environmental Medicine, Stockholm, Sweden. [54]Södersjukhuset, Department of Oncology, Stockholm, Sweden. [55]German Cancer Research Center (DKFZ), Molecular Genetics of Breast Cancer, Heidelberg, Germany. [56]Leuven Cancer Institute, University Hospitals Leuven, Leuven Multidisciplinary Breast Center, Department of Gynaecological Oncology, Leuven, Belgium. [57]Mayo Clinic, Department of Health Sciences Research, Rochester, MN, USA. [58]National University of Singapore and National University Health System, Saw Swee Hock School of Public Health, Singapore, Singapore. [59]National University Health System, Department of Surgery, Singapore, Singapore. [60]The University of Western Australia, School of Population and Global Health, Perth, Western Australia, Australia. [61]Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany. [62]University of Tübingen, Tübingen, Germany. [63]University of Oxford, Nuffield Department of Population Health, Oxford, UK. [64]Harvard T.H. Chan School of Public Health, Department of Epidemiology, Boston, MA, USA. [65]Aichi Cancer Center Research Institute, Division of Cancer Epidemiology and Prevention, Nagoya, Japan. [66]Nagoya University Graduate School of Medicine, Division of Cancer Epidemiology, Nagoya, Japan. [67]Erasmus MC Cancer Institute, Department of Medical Oncology, Rotterdam, The Netherlands. [68]MASA, Research Centre for Genetic Engineering and Biotechnology ‘Georgi D. Efremov’, Skopje, Republic of North Macedonia. [69]Pomeranian Medical University, Department of Genetics and Pathology, Szczecin, Poland. [70]Pomeranian Medical University, Independent Laboratory of Molecular Biology and Genetic Diagnostics, Szczecin, Poland. [71]University Hospital Ulm, Department of Gynaecology and Obstetrics, Ulm, Germany. [72]Seoul National University College of Medicine, Department of Preventive Medicine, Seoul, Korea. [73]University of Heidelberg, Faculty of Medicine, Heidelberg, Germany. [74]National Cancer Institute, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, Bethesda, MD, USA. [75]Harvard T.H. Chan School of Public Health, Program in Genetic Epidemiology and Statistical Genetics, Boston, MA, USA. [76]Oslo University Hospital and University of Oslo, Department of Medical Genetics, Oslo, Norway. [77]University of Oslo, Institute of Clinical Medicine, Faculty of Medicine, Oslo, Norway. [78]City of Hope, Department of Computational and Quantitative Medicine, Duarte, CA, USA. [79]City of Hope, City of Hope Comprehensive Cancer Center, Duarte, CA, USA. [80]VIB Center for Cancer Biology, Leuven, Belgium. [81]University of Leuven, Laboratory for Translational Genetics, Department of Human Genetics, Leuven, Belgium. [82]University of Hawaii Cancer Center, Epidemiology Program, Honolulu, HI, USA. [83]Genome Institute of Singapore, Human Genetics Division, Singapore, Singapore. [84]Karolinska Institutet, Department of Molecular Medicine and Surgery, Stockholm, Sweden. [85]Karolinska University Hospital, Department of Clinical Genetics, Stockholm, Sweden. [86]University of Eastern Finland, Institute of Clinical Medicine, Pathology and Forensic Medicine, Kuopio, Finland. [87]Kuopio University Hospital, Biobank of Eastern Finland, Kuopio, Finland. [88]Karolinska Institutet, Department of Clinical Science and Education, Södersjukhuset, Stockholm, Sweden. [89]Cancer Research

Malaysia, Breast Cancer Research Programme, Subang Jaya, Selangor, Malaysia. [90]University of Nottingham Malaysia Campus, Department of Mathematical Sciences, Faculty of Science and Engineering, Semenyih, Selangor, Malaysia. [91]University Hospital of Heraklion, Department of Medical Oncology, Heraklion, Greece. [92]University of Helsinki, Department of Obstetrics and Gynecology, Helsinki University Hospital, Helsinki, Finland. [93]Seoul National University College of Medicine, Department of Surgery, Seoul, Korea. [94]University Medical Center Hamburg-Eppendorf, Institute for Medical Biometry and Epidemiology, Hamburg, Germany. [95]University of North Carolina at Chapel Hill, Department of Epidemiology, Gillings School of Global Public Health and UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA. [96]King's College London, Research Oncology, Guy's Hospital, London, UK. [97]Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH & RC), Department of Basic Sciences, Lahore, Pakistan. [98]Carmel Medical Center and Technion Faculty of Medicine, Clalit National Cancer Control Center, Haifa, Israel. [99]Hospital Universitario Puerta de Hierro, Medical Oncology Department, Madrid, Spain. [100]University Hospital of Larissa, Department of Oncology, Larissa, Greece. [101]King's College London, School of Cancer & Pharmaceutical Sciences, Comprehensive Cancer Centre, Guy's Campus, London, UK. [102]University Hospital and German Cancer Research Center, National Center for Tumor Diseases, Heidelberg, Germany. [103]University of Heidelberg, Molecular Biology of Breast Cancer, University Womens Clinic Heidelberg, Heidelberg, Germany. [104]Academia Sinica, Institute of Biomedical Sciences, Taipei, Taiwan. [105]China Medical University, School of Public Health, Taichung, Taiwan. [106]Vanderbilt University School of Medicine, Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Nashville, TN, USA. [107]The University of Melbourne, Department of Clinical Pathology, Melbourne, Victoria, Australia. [108]Weill Cornell Medicine, Department of Population Health Sciences, New York, NY, USA. [109]Leiden University Medical Center, Department of Surgery, Leiden, The Netherlands. [110]University of Birmingham, Institute of Cancer and Genomic Sciences, Birmingham, UK. [111]University of Oxford, Wellcome Trust Centre for Human Genetics and Oxford NIHR Biomedical Research Centre, Oxford, UK. [112]Pontificia Universidad Javeriana, Institute of Human Genetics, Bogota, Colombia. [113]Mayo Clinic, Department of Health Science Research, Division of Epidemiology, Rochester, MN, USA. [114]University of Oulu, Laboratory of Cancer Genetics and Tumor Biology, Cancer and Translational Medicine Research Unit, Biocenter Oulu, Oulu, Finland. [115]Northern Finland Laboratory Centre Oulu, Laboratory of Cancer Genetics and Tumor Biology, Oulu, Finland. [116]Uppsala University, Department of Surgical Sciences, Uppsala, Sweden. [117]Seoul National University College of Medicine, Seoul, Korea. [118]Armed Forces Capital Hospital, Seongnam, Korea. [119]Tri-Service General Hospital, National Defense Medical Center, Department of Surgery, Taipei, Taiwan. [120]Brigham and Women's Hospital and Harvard Medical School, Channing Division of Network Medicine, Department of Medicine, Boston, MA, USA. [121]Cancer Research Malaysia, Breast Cancer

Research Programme, Subang Jaya, Selangor, Malaysia. [122]University of Malaya, Department of Surgery, Faculty of Medicine, Kuala Lumpur, Malaysia. [123]The Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital, Division of Psychosocial Research and Epidemiology, Amsterdam, The Netherlands. [124]University Medical Center Hamburg-Eppendorf, Cancer Epidemiology Group, University Cancer Center Hamburg (UCCH), Hamburg, Germany.

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Table 1.

Characteristics of the breast cancer population based on data from 67 population-based and hospital-based studies.

Characteristics	Overall	ER+	ER−	Luminal A-like	Luminal B HER2-negative-like	Luminal B HER2-like	HER2-enriched-like	Triple negative
Number of women[a], n	121 435	81 885	22 257	33 633	8915	7976	4025	8856
Number of overall deaths, n	16 890	9941	4587	3039	1490	1127	849	1858
Number of breast cancer specific deaths, n	8554	4654	2511	1256	792	613	458	978
Clinical risk factors								
Age at diagnosis, y, median (IQR)	57 (48–65)	58 (49–66)	53 (44–62)	59 (50–67)	56 (46–65)	54 (45–64)	54 (46–62)	53 (44–63)
Missing, n	56							
Year of diagnosis, n (%)								
1961–1975	264 (0.2)	98 (0.1)	105 (0.5)	24 (0.1)	3 (0.0)	16 (0.2)	19 (0.5)	59 (0.7)
1976–1990	4271 (3.6)	1707 (2.2)	931 (4.3)	725 (2.2)	273 (3.1)	144 (1.8)	188 (4.7)	433 (5)
1991–2005	68 872 (58.8)	44 075 (55.6)	13 425 (61.4)	13 776 (41.8)	3559 (40.7)	3694 (47.4)	2029 (51.1)	4351 (49.8)
2006–2019	43 725 (37.3)	33 414 (42.1)	7406 (33.9)	18 465 (56.0)	4905 (56.1)	3943 (50.6)	1734 (43.7)	3898 (44.6)
Missing, n	4303							
Ethnicity, n (%)								
European	91 981 (84)	62 984 (84.7)	15 479 (75.4)	26 087 (85.8)	6534 (82.5)	5773 (77.2)	2617 (68.3)	6078 (76.7)
Hispanic American	866 (0.8)	554 (0.7)	179 (0.9)	225 (0.7)	46 (0.6)	78 (1.0)	26 (0.7)	104 (1.3)
African	1015 (0.9)	461 (0.6)	435 (2.1)	135 (0.4)	52 (0.7)	58 (0.8)	52 (1.4)	261 (3.3)
Asian	13 139 (12.0)	8397 (11.3)	3991 (19.5)	3033 (10.0)	1090 (13.8)	1416 (18.9)	1061 (27.7)	1263 (15.9)
Other	2516 (2.3)	1929 (2.6)	433 (2.1)	936 (3.1)	198 (2.5)	157 (2.1)	77 (2.0)	217 (2.7)
Missing, n	11 918							
Tumor size, n (%)								
≤2 cm	49 887 (61.5)	36 848 (63.2)	7746 (50.3)	17 873 (65.5)	3339 (46.0)	3055 (52.2)	1305 (44.6)	3147 (48.2)
>2 and ≤5cm	27 665 (34.1)	19 024 (32.7)	6706 (43.5)	8358 (30.6)	3449 (47.5)	2478 (42.4)	1374 (47.0)	3016 (46.2)
>5 cm	3603 (4.4)	2388 (4.1)	948 (6.2)	1067 (3.9)	472 (6.5)	317 (5.4)	245 (8.4)	371 (5.7)

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Characteristics	Overall	ER+	ER−	Luminal A-like	Luminal B HER2-negative-like	Luminal B HER2-like	HER2-enriched-like	Triple negative
Missing, n	40 280							
Nodal status, n (%)								
Negative	59 569 (62.1)	43 212 (62.0)	11 156 (59.6)	20 203 (63.5)	4352 (51.4)	3930 (54.6)	1795 (50.5)	4874 (62.7)
Positive	36 395 (37.9)	26 476 (38.0)	7551 (40.4)	11 609 (36.5)	4112 (48.6)	3264 (45.4)	1759 (49.5)	2905 (37.3)
Missing, n	25 471							
Tumor stage, n (%)								
I	34 157 (44.5)	25 351 (45.9)	5147 (34.6)	12 222 (47.7)	1903 (29.4)	2209 (37.5)	839 (28.0)	2143 (34.6)
II	34 696 (45.2)	24 498 (44.3)	7663 (51.5)	11 154 (43.5)	3567 (55.2)	2838 (48.1)	1561 (52.1)	3314 (53.5)
III	7990 (10.4)	5411 (9.8)	2056 (13.8)	2243 (8.8)	997 (15.4)	850 (14.4)	597 (19.9)	742 (12)
Missing, n	44 592							
Grade, n (%)								
Grade 1	17 919 (19.2)	15 546 (22.6)	800 (4.5)	10 130 (30.1)	-	672 (9.3)	62 (1.8)	279 (3.7)
Grade 2	45 065 (48.3)	37 347 (54.3)	4614 (26.1)	23 503 (69.9)	-	3397 (47.0)	918 (26.4)	1709 (22.4)
Grade 3	30 231 (32.4)	15 852 (23.1)	12 253 (69.4)	-	8915 (100)	3151 (43.6)	2498 (71.8)	5651 (74)
Missing, n	28 220							
Surgery, n (%)								
No surgery	1160 (1.6)	437 (0.8)	152 (1.1)	108 (0.4)	26 (0.4)	37 (0.7)	22 (0.8)	35 (0.6)
Breast conserving surgery	29 530 (40.9)	22 923 (44.4)	4971 (36.8)	11 551 (47.5)	2371 (36.7)	2188 (40.3)	775 (28.9)	2168 (38.8)
Mastectomy	22 785 (31.6)	16 032 (31.1)	5237 (38.7)	6730 (27.7)	2156 (33.4)	2092 (38.5)	1378 (51.3)	1821 (32.6)
Type unknown	18 677 (25.9)	12 187 (23.6)	3155 (23.3)	5942 (24.4)	1907 (29.5)	1111 (20.5)	510 (19.0)	1561 (27.9)
Missing, n	49 283							
Radiation therapy, n (%)								
No	18 563 (27.6)	12 525 (26.3)	3684 (28.8)	5268 (25.7)	1250 (22.8)	1353 (26.1)	801 (30.8)	1217 (25.7)
Yes	48 616 (72.4)	35 037 (73.7)	9111 (71.2)	15 241 (74.3)	4243 (77.2)	3826 (73.9)	1797 (69.2)	3510 (74.3)
Missing, n	54 256							
Chemotherapy, n (%)								
No	27 667 (41.0)	21 895 (45.9)	2310 (16.5)	11 812 (53.0)	1632 (25.3)	1203 (21.9)	328 (11.3)	864 (15.2)

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Characteristics	Overall	ER+	ER−	Luminal A-like	Luminal B HER2-negative-like	Luminal B HER2-like	HER2-enriched-like	Triple negative
Yes	39 815 (59.0)	25 796 (54.1)	11 729 (83.5)	10 465 (47.0)	4820 (74.7)	4294 (78.1)	2584 (88.7)	4816 (84.8)
Missing, n	53 953							
Endocrine therapy, n (%)								
No	19 688 (28.6)	7869 (15.6)	9232 (77.4)	3629 (15.5)	781 (13.1)	978 (17.2)	2209 (88.0)	3907 (84.5)
Yes	49 163 (71.4)	42 682 (84.4)	2689 (22.6)	19 859 (84.5)	5175 (86.9)	4702 (82.8)	302 (12.0)	717 (15.5)
Missing, n	52 584							
Trastuzumab, n (%)								
No	50 545 (95.1)	33 531 (95.4)	10 337 (91.6)	16 909 (99.7)	4849 (99.4)	2341 (60.9)	1306 (61.9)	5104 (99.6)
Yes	2598 (4.9)	1607 (4.6)	952 (8.4)	53 (0.3)	30 (0.6)	1505 (39.1)	805 (38.1)	18 (0.4)
Missing, n	68 292							
Reproductive and lifestyle risk factors								
Age at menarche, median (IQR)	13 (12–14)	13 (12–14)	13 (12–14)	13 (12–14)	13 (12–14)	13 (12–14)	13 (12–14)	13 (12–14)
Missing, n	35 355							
Parity, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
Nulliparous, n (%)	12 932 (14.0)	8971 (14.2)	2066 (12.9)	3633 (14.1)	934 (15.0)	870 (15.0)	384 (13.5)	787 (12.8)
Parous, n (%)	79 415 (86.0)	54 292 (85.8)	13 955 (87.1)	22 162 (85.9)	5291 (85.0)	4928 (85.0)	2456 (86.5)	5376 (87.2)
Missing, n	29 088							
Age at first full term pregnancy[b], median (IQR)	25 (22–28)	25 (22–28)	24 (21–28)	24 (21–28)	25 (22–28)	25 (22–29)	25 (22–28)	24 (21–27)
Missing, n	50 965							
Breastfeeding, n (%)								
Never	24 906 (39.5)	16 660 (38.4)	4476 (39.9)	7039 (39.2)	1754 (41.9)	1716 (40.2)	831 (41.3)	1796 (42.5)
Ever	38 195 (60.5)	26 730 (61.6)	6734 (60.1)	10 912 (60.8)	2435 (58.1)	2555 (59.8)	1181 (58.7)	2433 (57.5)
Missing, n	58 334							
Duration in months[c], median (IQR)	7 (3–15)	7 (3–15)	7 (3–16)	7 (3–15)	7 (3–15)	7 (3–15)	8 (3–17)	6 (3–15)
Missing, n	68 870							

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Characteristics	Overall	ER+	ER−	Luminal A-like	Luminal B HER2-negative-like	Luminal B HER2-like	HER2-enriched-like	Triple negative
Time since last full term birth[b,†], n (%)								
≥ 10 years	29 200 (64.2)	18 626 (63.3)	5795 (65.7)	7901 (65.5)	1822 (62.0)	1986 (63.0)	1096 (67.8)	2303 (67.3)
5 – 10 years	1926 (4.2)	1115 (3.8)	466 (5.3)	362 (3.0)	103 (3.5)	177 (5.6)	65 (4.0)	163 (4.8)
0 – 5 years	1179 (2.6)	601 (2.0)	393 (4.5)	161 (1.3)	70 (2.4)	101 (3.2)	51 (3.2)	130 (3.8)
Missing, n	75 975							
Oral contraceptives, n (%)								
Never use	29 677 (44.5)	20 263 (45.0)	5090 (43.4)	8398 (46.4)	1967 (45.1)	2018 (43.6)	1096 (48.6)	1923 (43.2)
Ever use	37 070 (55.5)	24 799 (55.0)	6629 (56.6)	9701 (53.6)	2395 (54.9)	2608 (56.4)	1159 (51.4)	2533 (56.8)
Missing, n	54 688							
Menopausal hormone therapy[‡], n (%)								
Never use, postmenopausal	28 534 (37.1)	20 062 (38.3)	5088 (37.1)	9129 (41.4)	2315 (42.8)	2044 (39.0)	1108 (43.3)	2115 (39.0)
Former[e] use estrogen therapy	1394 (1.8)	1041 (2.0)	195 (1.4)	397 (1.8)	81 (1.5)	77 (1.5)	40 (1.6)	91 (1.7)
Former[e] use estrogen+progestin	1414 (1.8)	1035 (2.0)	246 (1.8)	490 (2.2)	91 (1.7)	94 (1.8)	49 (1.9)	124 (2.3)
Former[e] use (unknown type)	5972 (7.8)	4366 (8.3)	912 (6.7)	1960 (8.9)	481 (8.9)	291 (5.6)	164 (6.4)	405 (7.5)
Current[f] use estrogen therapy	2175 (2.8)	1456 (2.8)	272 (2.0)	562 (2.5)	103 (1.9)	129 (2.5)	48 (1.9)	119 (2.2)
Current[f] use estrogen+progestin	3755 (4.9)	2689 (5.1)	458 (3.3)	1251 (5.7)	181 (3.3)	287 (5.5)	79 (3.1)	205 (3.8)
Current[f] use (unknown type)	5854 (7.6)	4398 (8.4)	647 (4.7)	1896 (8.6)	300 (5.5)	247 (4.7)	102 (4.0)	236 (4.4)
Missing, n	44 547							
BMI[d], median (IQR)	25 (23–28)	25 (23–29)	25 (22–28)	25 (23–29)	26 (23–29)	25 (22–28)	25 (22–28)	25 (23–29)
18.5–25 kg/m^2, n (%)	43 302 (47.4)	29 382 (46.9)	7716 (47.9)	11 545 (44.2)	2813 (42.8)	2962 (49.4)	1428 (49.4)	2925 (45.8)
<18.5 kg/m^2, n (%)	1657 (1.8)	1103 (1.8)	355 (2.2)	405 (1.6)	117 (1.8)	143 (2.4)	72 (2.5)	132 (2.1)
25–30 kg/m^2, n (%)	29 960 (32.8)	20 776 (33.2)	5134 (31.9)	8939 (34.2)	2210 (33.6)	1857 (31.0)	933 (32.3)	2041 (32.0)
>=30 kg/m^2, n (%)	16 435 (18.0)	11 353 (18.1)	2891 (18.0)	5228 (20.0)	1430 (21.8)	1034 (17.2)	459 (15.9)	1284 (20.1)
Missing, n	30 081							
Adult height, median (IQR)	163 (158–168)	163 (159–168)	163 (158–168)	163 (159–168)	163 (158–168)	163 (158–168)	162 (157–167)	163 (158–168)

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Characteristics	Overall	ER+	ER−	Luminal A-like	Luminal B HER2-negative-like	Luminal B HER2-like	HER2-enriched-like	Triple negative
Missing, n	33 481							
Smoking, n (%)								
Never	39 512 (59.0)	27 175 (59.3)	7352 (63.3)	11 767 (60.1)	2795 (62.4)	2961 (64.3)	1581 (68.7)	2856 (64.0)
Former[g]	17 407 (26.0)	12 082 (26.3)	2424 (20.9)	4954 (25.3)	1093 (24.4)	1069 (23.2)	387 (16.8)	903 (20.2)
Current[h]	10 073 (15.0)	6605 (14.4)	1840 (15.8)	2850 (14.6)	589 (13.2)	575 (12.5)	332 (14.4)	701 (15.7)
Missing, n	54 443							
Pack-years of smoking								
Former smokers[g], median (IQR)	0.8 (0.3–1.8)	0.8 (0.3–1.8)	0.7 (0.2–1.6)	0.9 (0.3–1.9)	0.8 (0.2–1.8)	0.7 (0.2–1.8)	0.6 (0.2–1.7)	0.7 (0.2–1.6)
Current smokers[h], median (IQR)	1.9 (0.9–3.1)	1.9 (1.0–3.1)	1.5 (0.7–2.6)	2.0 (0.9–3.2)	2.0 (1.0–3.1)	1.6 (0.7–2.5)	1.6 (0.8–2.7)	1.5 (0.6–2.6)
Missing, n	62 214							
Alcohol consumption[h], g/week, median (IQR)	14.7 (0.0–57.3)	16.0 (0.0–59.5)	10.8 (0.0–50.7)	12.0 (0.0–51.8)	12.0 (0.0–49.7)	15.0 (0.0–60.0)	6.0 (0.0–48.3)	6.0 (0.0–45.0)
Missing, n	100 522							
Cumulative alcohol consumption, g/day, median (IQR)	1.9 (0.0–7.9)	2.0 (0.0–8.2)	1.1 (0.0–6.1)	2.0 (0.0–8.4)	1.7 (0.0–7.0)	2.1 (0.0–7.8)	0.8 (0.0–5.6)	1.0 (0.0–5.7)
Missing, n	102 451							
Physical activity[h,i], median (IQR)	3 (1–8)	3 (1–9)	3 (1–8)	5 (1–11)	4 (2–11)	4 (1–9)	4 (1–9)	4 (1–10)
< 1.8 hours/week, n (%)	7103 (33.3)	4643 (31.6)	1043 (31.1)	1564 (27.1)	305 (24.6)	437 (28.2)	222 (29.1)	418 (31.0)
≥ 1.8 – < 5.5 hours/week, n (%)	7063 (33.1)	4679 (31.9)	1106 (33.0)	1545 (26.8)	424 (34.2)	491 (31.7)	231 (30.4)	382 (28.3)
≥ 5.5 hours/week, n (%)	7154 (33.6)	5363 (36.5)	1205 (35.9)	2656 (46.1)	510 (41.2)	619 (40.1)	308 (40.5)	549 (40.7)
Missing, n	100 115							

Percentages shown in the table might not sum up to 100% due to rounding.

[a]Numbers for subtypes do not add to total due to missing.

[b]For parous women only.

[c]For women who breastfed only.

[d] BMI at interview.

[e] More than 6 months before diagnosis.

[f] At diagnosis or within 6 months before diagnosis.

[g] More than 1 year before diagnosis.

[h] At diagnosis or within 1 year before diagnosis.

[i] Categories based on the tertiles of the observed distribution of the variable.

[†] Numbers are for parous women, excluding those who had a post-diagnosis last full-term birth, while percentages are computed based on all women with non-missing values, including nulliparous and women who had a post-diagnosis full-term birth.

[‡] Numbers are for postmenopausal women, while percentages are computed based on all women with non-missing values, including pre/perimenopausal women.

Table 2.

Associations between individual risk factors and 10 years all-cause mortality by ER status and intrinsic-like subtype based on the imputed datasets.

Risk factor	Overall	ER+	ER−	Luminal A-like	Luminal B HER2-negative-like	Luminal B HER2-positive-like	HER2-enriched-like	Triple negative
	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)
Age at menarche, per 1 year increase	2.3E-01 1.02 (1.00,1.04)	5.9E-01 1.01 (0.99,1.03)	8.0E-02 1.03 (1.00,1.06)	9.1E-01 1.00 (0.98,1.03)	6.9E-01 1.01 (0.98,1.04)	2.3E-01 1.03 (0.99,1.07)	2.4E-01 1.04 (0.99,1.09)	2.2E-01 1.03 (0.99,1.07)
Parity	1.4E-03	1.3E-04	1.5E-01	7.6E-04	1.4E-01	6.2E-01	9.1E-01	5.6E-02
0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1	0.87 (0.79,0.96)	0.87 (0.79,0.97)	0.85 (0.73,0.98)	0.86 (0.75,0.99)	0.88 (0.76,1.02)	0.91 (0.75,1.11)	0.87 (0.66,1.15)	0.80 (0.67,0.96)
2	0.86 (0.77,0.96)	0.83 (0.74,0.93)	0.92 (0.80,1.06)	0.81 (0.70,0.93)	0.86 (0.73,1.01)	0.87 (0.71,1.06)	1.00 (0.76,1.31)	0.84 (0.71,1.00)
3	0.90 (0.82,1.00)	0.88 (0.79,0.98)	0.92 (0.79,1.06)	0.86 (0.76,0.98)	0.90 (0.77,1.06)	0.92 (0.74,1.14)	0.97 (0.75,1.25)	0.86 (0.71,1.05)
4+	0.97 (0.88,1.06)	0.92 (0.83,1.02)	1.05 (0.90,1.23)	0.89 (0.78,1.02)	0.94 (0.79,1.12)	1.01 (0.80,1.29)	1.06 (0.80,1.41)	0.99 (0.80,1.24)
Age at first full term pregnancy[a], years	1.9E−14	2.5E−11	1.5E−02	4.3E−07	2.6E−02	4.3E−03	5.7E−01	3.9E−02
< 20	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
20 to < 25	0.88 (0.83,0.94)	0.86 (0.80,0.93)	0.93 (0.83,1.04)	0.84 (0.76,0.93)	0.92 (0.80,1.07)	0.83 (0.69,1.00)	0.94 (0.71,1.23)	0.91 (0.79,1.04)
25 to < 30	0.82 (0.76,0.87)	0.80 (0.73,0.86)	0.87 (0.77,0.99)	0.78 (0.70,0.87)	0.82 (0.71,0.95)	0.79 (0.65,0.97)	0.89 (0.67,1.17)	0.86 (0.73,1.01)
≥ 30	0.79 (0.73,0.86)	0.78 (0.71,0.87)	0.82 (0.71,0.96)	0.79 (0.68,0.91)	0.83 (0.70,1.00)	0.73 (0.58,0.91)	0.80 (0.58,1.10)	0.82 (0.69,0.98)
Time since last full term birth[a], years	9.5E−02	4.5E−04	7.5E−01	8.8E−03	7.6E−01	2.0E−01	8.1E−01	6.4E−01
≥ 10	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
≥ 5 – < 10	1.07 (0.96,1.19)	1.15 (1.01,1.33)	0.95 (0.81,1.12)	1.16 (0.98,1.38)	1.10 (0.83,1.45)	1.17 (0.92,1.50)	0.99 (0.73,1.34)	0.88 (0.70,1.10)
> 0 – < 5	1.21 (1.03,1.41)	1.36 (1.12,1.65)	1.02 (0.82,1.26)	1.55 (1.08,2.24)	1.11 (0.83,1.48)	1.28 (0.86,1.91)	1.07 (0.76,1.51)	0.93 (0.68,1.27)
Breastfeeding[a]								
Per 6 months increase	2.4E−01 1.02 (0.99,1.04)	5.4E−01 1.01 (0.99,1.04)	1.2E−01 1.03 (1.00,1.06)	4.7E−01 1.01 (0.99,1.04)	7.2E−01 1.01 (0.97,1.06)	4.1E−01 1.02 (0.99,1.06)	6.7E−01 1.01 (0.97,1.05)	1.1E−01 1.03 (1.00,1.06)
Ever vs never	7.5E−01 0.97 (0.85,1.10)	6.2E−01 0.95 (0.84,1.08)	9.1E−01 1.01 (0.84,1.23)	5.1E−01 0.93 (0.81,1.08)	9.1E−01 0.99 (0.83,1.17)	7.3E−01 0.94 (0.76,1.17)	9.5E−01 0.99 (0.75,1.31)	9.0E−01 1.02 (0.85,1.22)

Risk factor	Overall	ER+	ER−	Luminal A-like	Luminal B HER2-negative-like	Luminal B HER2-positive-like	HER2-enriched-like	Triple negative
	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)
BMI, kg/m^2								
All women	2.2E−02	5.9E−03	2.8E−01	5.9E−03	1.4E−01	1.6E−01	6.4E−01	3.2E−01
18.5 to < 25	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
< 18.5	1.34 (0.96,1.87)	1.41 (1.03,1.95)	1.24 (0.82,1.87)	1.56 (1.12,2.18)	1.32 (0.80,2.18)	1.17 (0.71,1.94)	1.22 (0.69,2.14)	1.20 (0.78,1.83)
25 to < 30	1.05 (0.92,1.21)	1.06 (0.94,1.20)	1.03 (0.86,1.24)	1.03 (0.90,1.18)	1.07 (0.92,1.26)	1.13 (0.96,1.33)	0.98 (0.80,1.20)	1.04 (0.86,1.27)
≥ 30	1.23 (1.09,1.40)	1.24 (1.10,1.39)	1.20 (1.01,1.43)	1.24 (1.09,1.41)	1.22 (1.04,1.42)	1.23 (1.01,1.50)	1.19 (0.92,1.55)	1.21 (1.02,1.43)
Postmenopausal women	2.5E−07	3.4E−06	2.0E−02	1.2E−05	1.2E−01	2.4E−01	5.3E−01	1.2E−01
18.5 to < 25	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
< 18.5	1.53 (1.30,1.80)	1.57 (1.30,1.89)	1.46 (1.09,1.95)	1.73 (1.41,2.12)	1.45 (0.89,2.38)	1.16 (0.67,2.00)	1.42 (0.80,2.50)	1.48 (1.03,2.13)
25 to < 30	1.05 (0.97,1.12)	1.06 (0.97,1.15)	1.02 (0.92,1.12)	1.02 (0.92,1.12)	1.09 (0.94,1.26)	1.16 (0.95,1.42)	0.95 (0.75,1.20)	1.02 (0.89,1.17)
≥ 30	1.20 (1.12,1.29)	1.22 (1.12,1.33)	1.15 (1.02,1.29)	1.21 (1.09,1.35)	1.20 (1.00,1.44)	1.20 (0.97,1.48)	1.19 (0.92,1.53)	1.14 (0.98,1.33)
Pre/perimenopausal women	5.4E−01	5.3E−01	6.9E−01	6.4E−01	6.2E−01	6.2E−01	9.1E−01	6.7E−01
18.5 to < 25	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
< 18.5	1.08 (0.53,2.21)	1.14 (0.54,2.41)	1.03 (0.49,2.19)	1.17 (0.49,2.80)	1.17 (0.54,2.52)	1.17 (0.46,2.95)	1.02 (0.41,2.55)	0.90 (0.36,2.22)
25 to < 30	1.07 (0.76,1.49)	1.06 (0.77,1.48)	1.06 (0.72,1.57)	1.08 (0.70,1.66)	1.04 (0.76,1.41)	1.06 (0.76,1.49)	1.02 (0.71,1.47)	1.09 (0.68,1.74)
≥ 30	1.32 (0.94,1.85)	1.32 (0.96,1.82)	1.30 (0.88,1.94)	1.36 (0.87,2.12)	1.28 (0.96,1.72)	1.34 (0.94,1.92)	1.18 (0.75,1.88)	1.35 (0.90,2.04)
Adult height, per 5 cm increase	3.7E−01 0.97 (0.92,1.02)	4.6E−01 0.97 (0.91,1.03)	3.0E−01 0.97 (0.92,1.02)	4.1E−01 0.97 (0.91,1.03)	6.7E−01 0.98 (0.91,1.05)	6.4E−01 0.97 (0.90,1.05)	3.4E−01 0.95 (0.87,1.03)	4.4E−01 0.97 (0.92,1.03)
Oral contraceptive use	1.6E−04	7.8E−04	2.6E−02	8.9E−04	2.6E−01	1.5E−01	2.7E−01	5.9E−02
Ever vs never	0.88 (0.84,0.93)	0.89 (0.84,0.94)	0.88 (0.80,0.96)	0.87 (0.81,0.93)	0.91 (0.81,1.03)	0.89 (0.79,1.01)	0.90 (0.77,1.04)	0.88 (0.78,0.98)
Menopausal hormone therapy	0.0E+00	0.0E+00	3.0E−09	0.0E+00	6.2E−05	3.1E−04	3.9E−02	3.5E−03
Never use, postmenopausal	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Former[b] use of ET	0.73 (0.64,0.84)	0.75 (0.65,0.88)	0.67 (0.48,0.93)	0.78 (0.64,0.94)	0.68 (0.49,0.94)	0.75 (0.50,1.13)	0.60 (0.27,1.31)	0.71 (0.46,1.10)
Former[b] use of EPT	0.81 (0.70,0.93)	0.80 (0.67,0.95)	0.89 (0.68,1.18)	0.75 (0.57,0.99)	0.86 (0.58,1.27)	0.77 (0.49,1.19)	0.97 (0.55,1.70)	0.93 (0.64,1.35)
Former[b] use (unknown type)	0.80 (0.75,0.85)	0.79 (0.74,0.85)	0.81 (0.71,0.94)	0.78 (0.70,0.86)	0.82 (0.68,1.01)	0.79 (0.63,0.99)	0.87 (0.66,1.15)	0.80 (0.68,0.94)

Risk factor	Overall	ER+	ER−	Luminal A-like	Luminal B HER2-negative-like	Luminal B HER2-positive-like	HER2-enriched-like	Triple negative
	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)
Current[c] use of ET	0.70 (0.61,0.79)	0.68 (0.59,0.79)	0.75 (0.58,0.97)	0.73 (0.60,0.88)	0.64 (0.42,0.97)	0.64 (0.42,0.95)	0.53 (0.29,0.99)	0.83 (0.59,1.17)
Current[c] use of EPT	0.58 (0.52,0.65)	0.59 (0.52,0.67)	0.56 (0.45,0.70)	0.59 (0.50,0.70)	0.57 (0.40,0.82)	0.55 (0.40,0.76)	0.53 (0.34,0.84)	0.64 (0.48,0.85)
Current[c] use (unknown type)	0.75 (0.69,0.82)	0.72 (0.65,0.80)	0.87 (0.71,1.06)	0.72 (0.64,0.82)	0.70 (0.56,0.88)	0.72 (0.53,0.99)	0.81 (0.54,1.23)	0.96 (0.73,1.27)
Smoking	0.0E+00	0.0E+00	3.5E−03	0.0E+00	3.5E−03	3.0E−02	1.6E−01	4.8E−02
Never	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Former[d]	1.01 (0.97,1.05)	1.04 (0.98,1.09)	0.97 (0.88,1.06)	1.05 (0.98,1.13)	0.99 (0.89,1.12)	1.00 (0.88,1.14)	1.07 (0.86,1.33)	0.94 (0.83,1.05)
Current[e]	1.38 (1.30,1.45)	1.46 (1.37,1.56)	1.20 (1.10,1.32)	1.59 (1.48,1.71)	1.31 (1.14,1.50)	1.28 (1.09,1.50)	1.28 (1.04,1.59)	1.20 (1.04,1.37)
No. of pack-years of smoking, per 10 units increase	1.2E−03 1.11 (1.06,1.15)	1.2E−03 1.12 (1.07,1.17)	3.0E−03 1.08 (1.04,1.12)	5.0E−04 1.13 (1.08,1.18)	2.2E−02 1.10 (1.03,1.16)	1.9E−02 1.09 (1.03,1.15)	2.2E−02 1.10 (1.03,1.17)	2.2E−02 1.07 (1.03,1.12)
Alcohol consumption[e], per 10 g/week	8.8E−01 1.01 (0.99,1.01)	9.0E−01 1.00 (0.99,1.01)	8.8E−01 1.00 (0.99,1.01)	9.9E−01 1.00 (0.99,1.01)	8.4E−01 1.00 (0.99,1.01)	7.5E−01 1.00 (0.98,1.01)	9.1E−01 1.00 (0.99,1.02)	8.1E−01 1.00 (0.98,1.01)
Cumulative alcohol consumption, per 10 g/day	8.0E−01 1.01 (0.96,1.06)	7.8E−01 1.01 (0.96,1.06)	8.7E−01 1.01 (0.96,1.06)	7.5E−01 1.01 (0.96,1.07)	9.0E−01 1.01 (0.94,1.08)	9.1E−01 1.01 (0.95,1.06)	6.9E−01 1.02 (0.96,1.08)	9.1E−01 1.00 (0.94,1.07)
Physical activity[e,f], hours/week	8.3E−02	9.6E−02	8.2E−02	1.1E−01	2.1E−01	8.4E−03	6.1E−02	1.4E−01
< 1.8	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
≥ 1.8 – < 5.5	0.80 (0.38,1.68)	0.80 (0.38,1.70)	0.79 (0.38,1.65)	0.77 (0.33,1.80)	0.85 (0.40,1.81)	0.84 (0.55,1.28)	0.87 (0.52,1.46)	0.76 (0.29,1.97)
≥ 5.5	0.42 (0.21,0.85)	0.42 (0.20,0.88)	0.42 (0.20,0.85)	0.40 (0.18,0.89)	0.47 (0.21,1.06)	0.44 (0.27,0.71)	0.46 (0.25,0.87)	0.40 (0.18,0.90)

All the analyses were stratified by study and adjusted for lymph nodes status, tumor size, tumor grade and (neo)adjuvant systemic treatment. Age of the patients was used as time scale. Reported p-values (P) are from likelihood ratio tests comparing a model with and without a particular risk factor and are adjusted for multiple testing using the Benjamini-Hochberg method for false discovery rate (FDR) control on 136 tests. Heterogeneity test by subtype is shown in Table 3. Numbers of patients and events included in the corresponding complete-case analyses are shown in Supplementary Figures S1 (overall), S3 (ER+), S5 (ER−), S7 (Luminal A-like), S9 (Luminal B-HER2-negative-like), S11 (Luminal B-HER2-positive-like), S13 (HER2-enriched), and S15 (triple negative). Abbreviations: ET: estrogen therapy; EPT: combined estrogen and progestin therapy.

[a]Association estimated in parous women.

[b]More than 6 months before diagnosis.

[c]At diagnosis or within 6 months before diagnosis.

[d] More than 1 year before diagnosis.

[e] At diagnosis or within 1 year before diagnosis.

[f] Categories based on the tertiles of the observed distribution of the variable.

Table 3.

Heterogeneity tests of the associations between risk factors and outcomes (10-year all-cause mortality and breast cancer-specific mortality), by ER status and by intrinsic-like subtype.

Risk factor	All-cause mortality		Breast cancer specific mortality	
	ER status	Intrinsic-like subtype[e]	ER status	Intrinsic-like subtype[e]
	P	P	P	P
Age at menarche	6.7E−01	8.6E−01	7.2E−01	1.0E+00
Parity	8.1E−01	1.0E+00	7.2E−01	1.0E+00
Age at first full term pregnancy[a]	6.7E−01	1.0E+00	7.2E−01	1.0E+00
Time since last full term birth[a]	8.5E−01	1.0E+00	5.4E−01	3.3E−01
Breastfeeding[a]	7.8E−01	9.7E−01	1.0E+00	1.0E+00
Duration of breastfeeding[a]	7.8E−01	1.0E+00	1.0E+00	1.0E+00
BMI (all women)	1.0E+00	1.0E+00	1.0E+00	1.0E+00
BMI (postmenopausal women)	1.0E+00	1.0E+00	1.0E+00	1.0E+00
BMI (pre/perimenopausal women)	1.0E+00	1.0E+00	1.0E+00	1.0E+00
Height	1.0E+00	1.0E+00	1.0E+00	1.0E+00
Oral contraceptive use	6.7E−01	6.7E−01	7.2E−01	1.0E+00
Menopausal hormone therapy[b,c]	1.0E+00	8.1E−01	1.0E+00	1.0E+00
Smoking	6.7E−01	6.7E−01	1.0E+00	1.0E+00
No. of pack-years of smoking	6.7E−01	6.7E−01	1.0E+00	1.0E+00
Alcohol consumption[d]	1.0E+00	1.0E+00	1.0E+00	1.0E+00
Cumulative alcohol consumption	1.0E+00	1.0E+00	1.0E+00	1.0E+00
Physical activity[d]	1.0E+00	1.0E+00	1.0E+00	1.0E+00

Reported p-values come from a likelihood ratio test comparing a model including the ER status/subtype variable and an interaction term between such variable and a specific risk factor, with a model without the interaction term. ER negative was used as the reference category for ER status and luminal A as the reference category for the subtype variable. P-values are adjusted for multiple testing using the Benjamini-Hochberg method for false discovery rate (FDR) control on 17 × 2 = 34 tests for each endpoint of interest (all-cause and breast cancer-specific mortality). All models have been stratified by study and adjusted for lymph nodes status, tumor size, tumor grade and (neo)adjuvant systemic treatment. Age of the patients was used as time scale.

[a]Association estimated in parous women.

[b] Former use of MHT was more than 6 months before diagnosis.

[c] Current use of MHT was at diagnosis or within 6 months before diagnosis.

[d] At diagnosis or within 1 year before diagnosis.

[e] Definition of intrinsic-like subtype follows Goldhirsch et al. 2011 as in Table 2 and Table 4.

Table 4.

Associations between individual risk factors and 10-year breast cancer-specific mortality by ER status and intrinsic-like subtype based on the imputed datasets.

Risk factor	Overall	ER+	ER−	Luminal A-like	Luminal B HER2-negative-like	Luminal B HER2-like	HER2-enriched-like	Triple negative
	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)
Age at menarche, per 1 year increase	2.0E−01 1.02 (1.00,1.05)	6.1E−01 1.01 (0.99,1.04)	8.0E−02 1.04 (1.01,1.08)	6.7E−01 1.02 (0.98,1.05)	9.2E−01 1.00 (0.96,1.04)	4.8E−01 1.04 (0.99,1.09)	2.8E−01 1.06 (1.00,1.11)	4.8E−01 1.03 (0.99,1.08)
Parity	6.3E−01	3.3E−01	7.1E−01	7.8E−01	5.4E−01	1.0E+00	9.6E−01	8.7E−01
0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1	0.95 (0.87,1.04)	0.94 (0.85,1.05)	0.95 (0.80,1.12)	0.96 (0.82,1.13)	0.87 (0.73,1.04)	1.04 (0.78,1.39)	0.92 (0.68,1.23)	0.92 (0.73,1.16)
2	0.93 (0.86,1.02)	0.88 (0.80,0.97)	1.03 (0.88,1.21)	0.89 (0.76,1.03)	0.87 (0.74,1.03)	0.96 (0.75,1.22)	1.04 (0.77,1.40)	0.98 (0.80,1.20)
3	0.98 (0.89,1.07)	0.96 (0.86,1.06)	1.00 (0.83,1.19)	0.97 (0.83,1.14)	0.90 (0.75,1.08)	1.02 (0.78,1.34)	1.05 (0.78,1.41)	0.95 (0.75,1.19)
4+	1.06 (0.95,1.19)	0.98 (0.86,1.11)	1.21 (1.01,1.46)	1.01 (0.85,1.21)	0.96 (0.76,1.22)	1.01 (0.73,1.40)	1.17 (0.79,1.74)	1.17 (0.90,1.52)
Age at first full term pregnancy[a], years	5.0E−05	2.8E−03	5.2E−01	2.0E−01	2.6E−01	6.1E−01	7.2E−01	7.6E−01
< 20	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
20 – < 25	0.90 (0.82,0.98)	0.88 (0.78,0.98)	0.95 (0.82,1.08)	0.87 (0.75,1.01)	0.89 (0.73,1.08)	0.88 (0.67,1.15)	0.92 (0.67,1.26)	0.95 (0.80,1.13)
25 – < 30	0.86 (0.79,0.94)	0.85 (0.76,0.96)	0.91 (0.79,1.05)	0.87 (0.73,1.04)	0.81 (0.66,0.99)	0.86 (0.65,1.12)	0.85 (0.63,1.14)	0.91 (0.76,1.10)
≥ 30	0.83 (0.76,0.91)	0.82 (0.72,0.93)	0.87 (0.74,1.03)	0.83 (0.68,1.00)	0.82 (0.65,1.03)	0.81 (0.59,1.10)	0.81 (0.55,1.18)	0.88 (0.70,1.11)
Time since last full term birth[a], years	4.6E−02	2.2E−04	7.7E−01	5.5E−03	6.7E−01	4.1E−01	8.7E−01	6.5E−01
≥ 10	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
≥ 5 – < 10	1.10 (0.96,1.27)	1.24 (1.07,1.44)	0.92 (0.73,1.18)	1.25 (1.03,1.53)	1.16 (0.90,1.51)	1.23 (0.91,1.66)	1.05 (0.67,1.65)	0.82 (0.59,1.14)
> 0 – < 5	1.28 (1.11,1.49)	1.49 (1.22,1.81)	1.03 (0.83,1.29)	1.79 (1.27,2.51)	1.21 (0.85,1.70)	1.37 (0.95,1.99)	1.14 (0.75,1.74)	0.90 (0.65,1.24)
Breastfeeding[a]								
Per 6 months increase	4.6E−01 1.03 (0.99,1.06)	5.4E−01 1.02 (0.99,1.05)	4.1E−01 1.03 (1.00,1.07)	4.6E−01 1.03 (0.99,1.06)	7.2E−01 1.02 (0.97,1.07)	7.2E−01 1.02 (0.97,1.07)	6.8E−01 1.03 (0.96,1.11)	4.8E−01 1.03 (0.99,1.07)

Risk factor	Overall	ER+	ER−	Luminal A-like	Luminal B HER2-negative-like	Luminal B HER2-like	HER2-enriched-like	Triple negative
	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)
Ever vs Never	9.2E−01 1.02 (0.85,1.22)	9.7E−01 1.01 (0.84,1.20)	8.7E−01 1.05 (0.83,1.32)	9.7E−01 0.99 (0.80,1.23)	9.7E−01 0.99 (0.81,1.22)	8.7E−01 0.95 (0.71,1.26)	9.2E−01 1.04 (0.70,1.55)	7.2E−01 1.09 (0.89,1.34)
BMI, kg/m^2								
All women	3.0E−01	2.6E−01	6.4E−01	4.8E−01	7.2E−01	4.6E−01	8.7E−01	7.8E−01
18.5 – < 25	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
< 18.5	1.12 (0.78,1.60)	1.13 (0.76,1.66)	1.11 (0.73,1.68)	1.04 (0.66,1.65)	1.27 (0.74,2.17)	1.20 (0.65,2.23)	1.10 (0.52,2.31)	0.99 (0.56,1.73)
25 – < 30	1.07 (0.92,1.23)	1.09 (0.95,1.25)	1.03 (0.87,1.23)	1.07 (0.90,1.29)	1.06 (0.90,1.25)	1.16 (0.93,1.44)	0.96 (0.74,1.25)	1.05 (0.86,1.28)
≥ 30	1.19 (1.05,1.34)	1.19 (1.04,1.37)	1.16 (1.01,1.34)	1.21 (1.03,1.43)	1.12 (0.95,1.31)	1.27 (0.99,1.63)	1.19 (0.91,1.55)	1.15 (0.96,1.38)
Postmenopausal women	5.7E−02	1.2E−01	4.8E−01	5.4E−01	8.7E−01	4.8E−01	7.8E−01	7.8E−01
18.5 – < 25	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
< 18.5	1.25 (0.98,1.59)	1.14 (0.84,1.56)	1.43 (0.99,2.06)	1.11 (0.66,1.84)	1.12 (0.46,2.68)	1.19 (0.52,2.71)	1.40 (0.64,3.07)	1.38 (0.79,2.39)
25 to < 30	1.08 (0.98,1.20)	1.12 (0.99,1.26)	1.02 (0.89,1.18)	1.08 (0.92,1.26)	1.10 (0.91,1.34)	1.25 (0.99,1.57)	0.93 (0.67,1.29)	1.05 (0.87,1.28)
≥ 30	1.15 (1.04,1.27)	1.17 (1.02,1.33)	1.12 (0.97,1.30)	1.18 (1.00,1.40)	1.08 (0.83,1.40)	1.22 (0.91,1.65)	1.21 (0.89,1.65)	1.08 (0.88,1.34)
Pre/perimenopausal women	6.3E−01	6.1E−01	7.8E−01	7.2E−01	7.4E−01	7.1E−01	9.7E−01	7.7E−01
18.5 – < 25	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
< 18.5	0.97 (0.52,1.83)	1.07 (0.55,2.10)	0.87 (0.42,1.81)	0.89 (0.39,2.01)	1.42 (0.74,2.71)	1.20 (0.45,3.22)	0.82 (0.28,2.42)	0.63 (0.20,2.02)
25 – < 30	1.04 (0.80,1.35)	1.04 (0.80,1.35)	1.05 (0.76,1.46)	1.07 (0.74,1.57)	1.00 (0.77,1.29)	1.04 (0.74,1.46)	1.00 (0.69,1.46)	1.06 (0.72,1.55)
≥ 30	1.27 (1.01,1.59)	1.28 (1.02,1.63)	1.23 (0.92,1.64)	1.32 (0.94,1.85)	1.19 (0.91,1.56)	1.39 (0.94,2.05)	1.14 (0.74,1.76)	1.27 (0.93,1.73)
Adult height, per 5 cm increase	9.6E−01 1.00 (0.95,1.05)	8.8E−01 0.99 (0.94,1.05)	9.0E−01 1.01 (0.95,1.07)	8.7E−01 0.99 (0.93,1.05)	1.0E+00 1.00 (0.94–1.06)	1.0E+00 1.00 (0.93,1.07)	8.7E−01 0.98 (0.90,1.08)	8.7E−01 1.02 (0.95,1.09)
Oral contraceptive use	3.3E−01	5.9E−01	3.3E−01	6.1E−01	8.7E−01	6.1E−01	7.2E−01	4.1E−01
Ever vs never	0.93 (0.86,1.00)	0.94 (0.87,1.03)	0.89 (0.79,1.00)	0.94 (0.83,1.05)	0.96 (0.80,1.16)	0.91 (0.77,1.07)	0.92 (0.76,1.12)	0.87 (0.75,1.02)
Menopausal hormone therapy	1.1E−10	4.3E−07	5.6E−03	1.9E−02	1.9E−01	5.2E−01	8.3E−01	4.6E−01
Never use, postmenopausal	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Former[b] use of ET	0.82 (0.66,1.02)	0.79 (0.61,1.03)	0.95 (0.65,1.38)	0.73 (0.47,1.15)	0.80 (0.49,1.30)	1.10 (0.61,1.99)	0.91 (0.40,2.10)	0.92 (0.57,1.50)
Former[b] use of EPT	1.06 (0.87,1.30)	1.01 (0.79,1.30)	1.20 (0.85,1.69)	0.96 (0.67,1.38)	1.11 (0.64,1.93)	0.97 (0.55,1.71)	1.16 (0.57,2.38)	1.24 (0.79,1.97)

Risk factor	Overall	ER+	ER−	Luminal A-like	Luminal B HER2-negative-like	Luminal B HER2-like	HER2-enriched-like	Triple negative
	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)	P HR (95% CI)
Former[b] use (unknown type)	0.87 (0.79,0.96)	0.87 (0.78,0.96)	0.91 (0.76,1.08)	0.85 (0.72,1.01)	0.87 (0.66,1.14)	0.83 (0.59,1.16)	0.93 (0.66,1.31)	0.90 (0.73,1.12)
Current[c] use of ET	0.69 (0.55,0.86)	0.69 (0.54,0.88)	0.69 (0.48,1.00)	0.71 (0.50,1.01)	0.59 (0.33,1.07)	0.68 (0.42,1.12)	0.63 (0.27,1.50)	0.78 (0.49,1.26)
Current[c] use of EPT	0.60 (0.51,0.72)	0.61 (0.49,0.75)	0.59 (0.44,0.79)	0.63 (0.48,0.83)	0.59 (0.37,0.93)	0.58 (0.38,0.87)	0.60 (0.31,1.14)	0.63 (0.42,0.95)
Current[c] use (unknown type)	0.83 (0.73,0.94)	0.80 (0.69,0.93)	0.94 (0.74,1.20)	0.81 (0.66,0.98)	0.75 (0.53,1.06)	0.81 (0.51,1.30)	0.89 (0.53,1.50)	1.02 (0.73,1.42)
Smoking	5.7E−02	1.2E−01	6.3E−01	2.0E−01	6.5E−01	8.7E−01	8.7E−01	6.7E−01
Never	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Former[d]	0.93 (0.87,0.99)	0.94 (0.86,1.03)	0.91 (0.81,1.03)	0.93 (0.83,1.05)	0.91 (0.80,1.04)	0.94 (0.78,1.13)	1.04 (0.81,1.34)	0.89 (0.75,1.05)
Current[e]	1.11 (1.02,1.21)	1.14 (1.04,1.26)	1.04 (0.90,1.21)	1.19 (1.03,1.36)	1.09 (0.89,1.32)	1.06 (0.84,1.33)	1.12 (0.81,1.55)	1.07 (0.87,1.33)
No. of pack-years of smoking, per 10 units increase	6.7E−01 1.02 (0.98,1.07)	6.7E−01 1.02 (0.97,1.08)	7.8E−01 1.01 (0.97,1.06)	6.7E−01 1.03 (0.97,1.09)	8.4E−01 1.02 (0.94,1.10)	8.0E−01 1.02 (0.95,1.09)	6.1E−01 1.05 (0.97,1.13)	9.2E−01 1.01 (0.94,1.07)
Alcohol consumption[e], per 10 g/week	9.0E−01 1.00 (0.99,1.01)	9.6E−01 1.00 (0.99,1.01)	8.7E−01 1.00 (0.99,1.01)	9.8E−01 1.00 (0.99,1.01)	8.7E−01 1.00 (0.99,1.01)	8.5E−01 1.00 (0.98,1.01)	8.8E−01 1.00 (0.99,1.01)	8.7E−01 1.00 (0.98,1.01)
Cumulative alcohol consumption, per 10 g/day	7.8E−01 0.98 (0.91,1.05)	7.8E−01 0.97 (0.89,1.07)	8.7E−01 0.99 (0.93,1.05)	7.3E−01 0.96 (0.87,1.07)	9.2E−01 0.99 (0.89,1.10)	7.2E−01 0.96 (0.88,1.06)	9.7E−01 1.01 (0.90,1.12)	8.7E−01 0.99 (0.92,1.06)
Physical activity[e,f], hours/week	5.2E−01	5.4E−01	5.2E−01	6.0E−01	6.5E−01	2.8E−01	5.2E−01	5.9E−01
< 1.8	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
≥ 1.8 – < 5.5	0.76 (0.21,2.73)	0.77 (0.21,2.81)	0.75 (0.21,2.67)	0.78 (0.19,3.22)	0.79 (0.20,3.07)	0.72 (0.28,1.85)	0.82 (0.28,2.42)	0.72 (0.17,3.15)
≥ 5.5	0.39 (0.13,1.17)	0.40 (0.13,1.19)	0.38 (0.12,1.21)	0.39 (0.12,1.26)	0.44 (0.13,1.49)	0.38 (0.16,0.88)	0.42 (0.15,1.12)	0.38 (0.11,1.31)

All analyses were stratified by study and adjusted for lymph nodes status, tumor size, tumor grade and (neo)adjuvant systemic treatment. Age of the patients was used as time scale. Reported p-values (P) are from likelihood ratio tests comparing a model with and without a particular risk factor and are adjusted for multiple testing using the Benjamini-Hochberg method for false discovery rate (FDR) control on 136 tests. Heterogeneity test by subtype is shown in Table 3. Numbers of patients and events included in the corresponding complete-case analyses are shown in Supplementary Figures S2 (overall), S4 (ER+), S6 (ER−), S8 (Luminal A-like), S10 (Luminal B HER2-negative-like), S12 (Luminal B HER2-positive-like), S14 (HER2-enriched-like), and S16 (triple negative).

Abbreviations: *ET*: estrogen therapy; *EPT*: combined estrogen and progestin therapy.

[a] Association estimated in parous women.

[b] More than 6 months before diagnosis.

[c] At diagnosis or within 6 months before diagnosis.

[d] More than 1 year before diagnosis.

[e] At diagnosis or within 1 year before diagnosis.

[f] Categories based on the tertiles of the observed distribution of the variable.

Table 5.

Multivariable Cox regression model on the imputed datasets including all risk factors simultaneously with 10-year all-cause mortality as endpoint.

Risk factor	HR (95% CI)	P-value
Age at menarche	1.02 (1.00, 1.04)	6.8E−02
Parity		
0	Ref.	
1	1.02 (0.91, 1.15)	7.4E−01
2	0.99 (0.86, 1.15)	9.0E−01
3	1.01 (0.86, 1.18)	9.4E−01
4+	1.01 (0.86, 1.18)	9.2E−01
Age at first full term pregnancy, years		
< 20	Ref.	
20 to < 25	0.90 (0.84, 0.96)	1.9E−03
25 to < 30	0.84 (0.78, 0.90)	2.8E−06
≥ 30	0.79 (0.72, 0.86)	2.0E−07
Time since last full term birth, years		
≥ 10	Ref.	
≥ 5 – < 10	1.13 (1.01, 1.28)	3.2E−02
> 0 – < 5	1.31 (1.11, 1.55)	1.1E−03
Breastfeeding		
Ever vs never	0.94 (0.82, 1.06)	2.7E−01
Duration of breastfeeding, per 6 months	1.02 (1.00, 1.04)	6.9E−02
BMI, kg/m^2		
18.5 to < 25	Ref.	
< 18.5	1.31 (0.96, 1.77)	5.6E−02
25 to < 30	1.04 (0.92, 1.18)	4.4E−01
≥ 30	1.19 (1.06, 1.34)	1.1E−03
Adult height, per 5 cm	0.98 (0.93, 1.03)	2.8E−01
Oral contraceptive use		
Ever vs never	0.91 (0.87, 0.96)	9.4E−05
Menopausal hormone therapy		
Never use, postmenopausal	Ref.	
Former[a] use of ET	0.75 (0.65, 0.86)	2.9E−05
Former[a] use of EPT	0.85 (0.73, 0.98)	3.0E−02
Former[a] use (unknown type)	0.81 (0.76, 0.86)	1.1E−11

Risk factor	HR (95% CI)	P-value
Current[b] use of ET	0.72 (0.64, 0.82)	8.3E−07
Current[b] use of EPT	0.61 (0.54, 0.69)	3.8E−15
Current[b] use (unknown type)	0.78 (0.72, 0.85)	4.9E−08
Smoking		
Never	Ref.	
Former[c]	1.03 (0.98, 1.07)	2.3E−01
Current[d]	1.37 (1.27, 1.47)	0.0E+00
Alcohol consumption[d], per 10 g/week	1.00 (0.99, 1.01)	6.6E−01
Cumulative alcohol consumption, per 10 g/day	1.00 (0.96, 1.05)	9.3E−01
Physical activity[d,e], hours/week		
< 1.8	Ref.	
≥ 1.8 – < 5.5	0.81 (0.39, 1.68)	5.2E−01
≥ 5.5	0.43 (0.21, 0.86)	6.3E−03

The Cox model was stratified by study and adjusted for lymph nodes status, tumor size, tumor grade, ER status, PR status, HER2 status and (neo)adjuvant systemic treatment. Age of the patients was used as time scale. All the risk factors were simultaneously included in the model. Corresponding complete-case analysis was based on 1264 cases and 158 deaths from all causes. A comparison between results from imputed data analysis and corresponding complete-case analysis are shown in Supplementary Figure S23.

[a] More than 6 months before diagnosis.

[b] At diagnosis or within 6 months before diagnosis.

[c] More than 1 year before diagnosis.

[d] At diagnosis or within a year before diagnosis.

[e] Categories based on the tertiles of the observed distribution of the variable. Abbreviations: *ET*: estrogen therapy; *EPT*: combined estrogen and progestin therapy.

Table 6.

Multivariable Cox regression model on the imputed datasets including all risk factors simultaneously, with 10-year breast cancer-specific mortality as endpoint.

Risk factor	HR (95% CI)	P-value
Age at menarche	1.03 (1.00, 1.05)	1.4E−02
Parity		
0	Ref.	
1	1.04 (0.90, 1.21)	5.5E−01
2	1.00 (0.83, 1.20)	1.0E+00
3	1.00 (0.81, 1.24)	1.0E+00
4+	1.01 (0.81, 1.25)	9.4E−01
Age at first full term pregnancy, years		
< 20	Ref.	
20 to < 25	0.90 (0.82, 0.99)	2.7E−02
25 to < 30	0.87 (0.79, 0.95)	2.8E−03
≥ 30	0.80 (0.72, 0.89)	4.4E−05
Time since last full term birth, years		
≥ 10	Ref.	
≥ 5 – < 10	1.16 (1.01, 1.34)	2.9E−02
> 0 – < 5	1.36 (1.15, 1.61)	2.4E−04
Breastfeeding		
Ever vs never	0.98 (0.81, 1.18)	8.2E−01
Duration of breastfeeding, per 6 months	1.02 (1.00, 1.05)	7.2E−02
BMI, kg/m^2		
18.5 to < 25	Ref.	
< 18.5	1.10 (0.79, 1.53)	5.6E−01
25 to < 30	1.06 (0.93, 1.20)	3.6E−01
≥ 30	1.16 (1.04, 1.29)	4.7E−03
Adult height, per 5 cm	1.00 (0.95, 1.06)	8.7E−01
Oral contraceptive use		
Ever vs never	0.96 (0.89, 1.03)	2.5E−01
Menopausal hormone therapy		
Never use, postmenopausal	Ref.	
Former[a] use of ET	0.82 (0.66, 1.03)	8.2E−02
Former[a] use of EPT	1.11 (0.91, 1.35)	3.2E−01
Former[a] use (unknown type)	0.88 (0.80, 0.97)	1.0E−02

Risk factor	HR (95% CI)	P-value
Current[b] use of ET	0.71 (0.57, 0.89)	2.6E−03
Current[b] use of EPT	0.64 (0.54, 0.76)	2.3E−07
Current[b] use (unknown type)	0.86 (0.76, 0.97)	1.3E−02
Smoking		
Never	Ref.	
Former[c]	0.94 (0.88, 1.01)	7.2E−02
Current[d]	1.11 (1.02, 1.21)	1.1E−02
Alcohol consumption[d], per 10 g/week	1.00 (0.99, 1.01)	8.4E−01
Cumulative alcohol consumption, per 10 g/day	0.98 (0.91, 1.06)	5.2E−01
Physical activity[d,e], hours/week		
< 1.8	Ref.	
≥ 1.8 – < 5.5	0.77 (0.22, 2.73)	6.4E−01
≥ 5.5	0.40 (0.13, 1.19)	5.7E−02

The Cox model is stratified by and adjusted for lymph nodes status, tumor size, tumor grade, ER status, PR status, HER2 status and (neo)adjuvant systemic treatment. Age of the patient was used as time scale. All risk factors were simultaneously included in the model. Corresponding complete-case analysis was based on 1264 cases and 114 deaths from breast cancer. A comparison between results from imputed data analysis and corresponding complete-case analysis are shown in Supplementary Figure S24.

[a] More than 6 months before diagnosis.

[b] At diagnosis or within 6 months before diagnosis.

[c] More than 1 year before diagnosis.

[d] At diagnosis or within a year before diagnosis.

[e] Categories based on the tertiles of the observed distribution of the variable. Abbreviations: *ET*: estrogen therapy; *EPT*: combined estrogen and progestin therapy.