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Published OnlineFirst January 26, 2021; DOI: 10.1158/1055-9965.EPI-20-0924

Breast Cancer Risk Factors and Survival by Tumor Subtype: Pooled Analyses from the Breast Cancer Association Consortium

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ABSTRACT

Background: It is not known whether 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 (8,554 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 ($P_{adj} > 0.30$). The strongest associations were between all-cause mortality and BMI ≥30 versus 18.5–25 kg/m^2 [HR (95% confidence interval (CI), 1.19 (1.06–1.34)]; current versus never smoking [1.37 (1.27–1.47)], high versus low physical activity [0.43 (0.21–0.86)], age ≥30 years versus <20 years at first pregnancy [0.79 (0.72–0.86)]; >0–<5 years versus ≥10 years since last full-term birth [1.31 (1.11–1.55)]; ever versus never use of oral contraceptives [0.91 (0.87–0.96)]; ever versus 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; for example, 1.11 (1.02–1.21) for current versus 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.

Published OnlineFirst January 26, 2021; DOI: 10.1158/1055-9965.EPI-20-0924

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Published OnlineFirst January 26, 2021; DOI: 10.1158/1055-9965.EPI-20-0924

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 patients with breast cancer (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). The 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; refs. 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 patients with breast cancer. 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 patients with invasive, stage I–III, female breast cancer 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 contraceptive use, MHT use, smoking status, pack-years of smoking, recent alcohol consumption, cumulative alcohol consumption, and physical activity. Exposure information was collected prediagnosis 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

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Cancer Epidemiol Biomarkers Prev 2021;30:623–42

doi: 10.1158/1055-9965.EPI-20-0924

Published OnlineFirst January 26, 2021; DOI: 10.1158/1055-9965.EPI-20-0924

single variable with eight 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 the date of diagnosis. Ever use of oral contraceptives was defined as use for ≥4 months and never use as <4 four months of use. There were three 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 1 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 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 vs. 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 10th 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 clinicopathologic 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 Tables S3 and S4; Supplementary Figs. 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 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. Because 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 with a prognostic model based only on the established breast cancer prognostic factors.

Results

There were 16,890 deaths overall and 8,554 breast cancer–related deaths after a follow-up time of 10 years in 121,435 patients with breast cancer (**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 [interquartile range (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 with nulliparous, with strongest associations observed in women who had one [HR (95% confidence interval (CI)), 0.87 (0.79–0.96)] or two 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 with <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 vs. ≥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 with normal weight women (BMI 18.5–25 kg/m^2). Low BMI was likewise associated with higher all-cause

Published OnlineFirst January 26, 2021; DOI: 10.1158/1055-9965.EPI-20-0924

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	8,915	7,976	4,025	8,856
Number of overall deaths, *n*	16,890	9,941	4,587	3,039	1,490	1,127	849	1,858
Number of breast cancer–specific deaths, *n*	8,554	4,654	2,511	1,256	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	4,271 (3.6)	1,707 (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)	3,559 (40.7)	3,694 (47.4)	2,029 (51.1)	4,351 (49.8)
2006–2019	43,725 (37.3)	33,414 (42.1)	7,406 (33.9)	18,465 (56.0)	4,905 (56.1)	3,943 (50.6)	1,734 (43.7)	3,898 (44.6)
Missing, *n*	4,303							
Ethnicity, *n* (%)								
European	91,981 (84)	62,984 (84.7)	15,479 (75.4)	26,087 (85.8)	6,534 (82.5)	5,773 (77.2)	2,617 (68.3)	6,078 (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	1,015 (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)	8,397 (11.3)	3,991 (19.5)	3,033 (10.0)	1,090 (13.8)	1,416 (18.9)	1,061 (27.7)	1,263 (15.9)
Other	2,516 (2.3)	1,929 (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)	7,746 (50.3)	17,873 (65.5)	3,339 (46.0)	3,055 (52.2)	1,305 (44.6)	3,147 (48.2)
>2 and ≤5 cm	27,665 (34.1)	19,024 (32.7)	6,706 (43.5)	8,358 (30.6)	3,449 (47.5)	2,478 (42.4)	1,374 (47.0)	3,016 (46.2)
>5 cm	3,603 (4.4)	2,388 (4.1)	948 (6.2)	1,067 (3.9)	472 (6.5)	317 (5.4)	245 (8.4)	371 (5.7)
Missing, *n*	40,280							
Nodal status, *n* (%)								
Negative	59,569 (62.1)	43,212 (62.0)	11,156 (59.6)	20,203 (63.5)	4,352 (51.4)	3,930 (54.6)	1,795 (50.5)	4,874 (62.7)
Positive	36,395 (37.9)	26,476 (38.0)	7,551 (40.4)	11,609 (36.5)	4,112 (48.6)	3,264 (45.4)	1,759 (49.5)	2,905 (37.3)
Missing, *n*	25,471							
Tumor stage, *n* (%)								
I	34,157 (44.5)	25,351 (45.9)	5,147 (34.6)	12,222 (47.7)	1,903 (29.4)	2,209 (37.5)	839 (28.0)	2,143 (34.6)
II	34,696 (45.2)	24,498 (44.3)	7,663 (51.5)	11,154 (43.5)	3,567 (55.2)	2,838 (48.1)	1,561 (52.1)	3,314 (53.5)
III	7,990 (10.4)	5,411 (9.8)	2,056 (13.8)	2,243 (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)	4,614 (26.1)	23,503 (69.9)	–	3,397 (47.0)	918 (26.4)	1,709 (22.4)
Grade 3	30,231 (32.4)	15,852 (23.1)	12,253 (69.4)	–	8,915 (100)	3,151 (43.6)	2,498 (71.8)	5,651 (74)
Missing, *n*	28,220							
Surgery, *n* (%)								
No surgery	1,160 (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)	4,971 (36.8)	11,551 (47.5)	2,371 (36.7)	2,188 (40.3)	775 (28.9)	2,168 (38.8)
Mastectomy	22,785 (31.6)	16,032 (31.1)	5,237 (38.7)	6,730 (27.7)	2,156 (33.4)	2,092 (38.5)	1,378 (51.3)	1,821 (32.6)
Type unknown	18,677 (25.9)	12,187 (23.6)	3,155 (23.3)	5,942 (24.4)	1,907 (29.5)	1,111 (20.5)	510 (19.0)	1,561 (27.9)
Missing, *n*	49,283							

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Published OnlineFirst January 26, 2021; DOI: 10.1158/1055-9965.EPI-20-0924

Table 1. Characteristics of the breast cancer population based on data from 67 population-based and hospital-based studies. (Cont'd)

Characteristics	Overall	ER$^+$	ER$^-$	Luminal A–like	Luminal B HER2-negative–like	Luminal B HER2–like	HER2-enriched–like	Triple negative
Radiotherapy, *n* (%)								
No	18,563 (27.6)	12,525 (26.3)	3,684 (28.8)	5,268 (25.7)	1,250 (22.8)	1,353 (26.1)	801 (30.8)	1,217 (25.7)
Yes	48,616 (72.4)	35,037 (73.7)	9,111 (71.2)	15,241 (74.3)	4,243 (77.2)	3,826 (73.9)	1,797 (69.2)	3,510 (74.3)
Missing, *n*	54,256							
Chemotherapy, *n* (%)								
No	27,667 (41.0)	21,895 (45.9)	2,310 (16.5)	11,812 (53.0)	1,632 (25.3)	1,203 (21.9)	328 (11.3)	864 (15.2)
Yes	39,815 (59.0)	25,796 (54.1)	11,729 (83.5)	10,465 (47.0)	4,820 (74.7)	4,294 (78.1)	2,584 (88.7)	4,816 (84.8)
Missing, *n*	53,953							
Endocrine therapy, *n* (%)								
No	19,688 (28.6)	7,869 (15.6)	9,232 (77.4)	3,629 (15.5)	781 (13.1)	978 (17.2)	2,209 (88.0)	3,907 (84.5)
Yes	49,163 (71.4)	42,682 (84.4)	2,689 (22.6)	19,859 (84.5)	5,175 (86.9)	4,702 (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)	4,849 (99.4)	2,341 (60.9)	1,306 (61.9)	5,104 (99.6)
Yes	2,598 (4.9)	1,607 (4.6)	952 (8.4)	53 (0.3)	30 (0.6)	1,505 (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)	8,971 (14.2)	2,066 (12.9)	3,633 (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)	5,291 (85.0)	4,928 (85.0)	2,456 (86.5)	5,376 (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)	4,476 (39.9)	7,039 (39.2)	1,754 (41.9)	1,716 (40.2)	831 (41.3)	1,796 (42.5)
Ever	38,195 (60.5)	26,730 (61.6)	6,734 (60.1)	10,912 (60.8)	2,435 (58.1)	2,555 (59.8)	1,181 (58.7)	2,433 (57.5)
Missing, *n*	58,334							
Duration in mo[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							
Time since last full-term birth[b,†], *n* (%)								
≥10 y	29,200 (64.2)	18,626 (63.3)	5,795 (65.7)	7,901 (65.5)	1,822 (62.0)	1,986 (63.0)	1,096 (67.8)	2,303 (67.3)
5–10 y	1,926 (4.2)	1,115 (3.8)	466 (5.3)	362 (3.0)	103 (3.5)	177 (5.6)	65 (4.0)	163 (4.8)
0–5 y	1,179 (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)	5,090 (43.4)	8,398 (46.4)	1,967 (45.1)	2,018 (43.6)	1,096 (48.6)	1,923 (43.2)
Ever use	37,070 (55.5)	24,799 (55.0)	6,629 (56.6)	9,701 (53.6)	2,395 (54.9)	2,608 (56.4)	1,159 (51.4)	2,533 (56.8)
Missing, *n*	54,688							
MHT[‡], *n* (%)								
Never use, postmenopausal	28,534 (37.1)	20,062 (38.3)	5,088 (37.1)	9,129 (41.4)	2,315 (42.8)	2,044 (39.0)	1,108 (43.3)	2,115 (39.0)
Former[e] use estrogen therapy	1,394 (1.8)	1,041 (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	1,414 (1.8)	1,035 (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)	5,972 (7.8)	4,366 (8.3)	912 (6.7)	1,960 (8.9)	481 (8.9)	291 (5.6)	164 (6.4)	405 (7.5)
Current[f] use estrogen therapy	2,175 (2.8)	1,456 (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	3,755 (4.9)	2,689 (5.1)	458 (3.3)	1,251 (5.7)	181 (3.3)	287 (5.5)	79 (3.1)	205 (3.8)
Current[f] use (unknown type)	5,854 (7.6)	4,398 (8.4)	647 (4.7)	1,896 (8.6)	300 (5.5)	247 (4.7)	102 (4.0)	236 (4.4)
Missing, *n*	44,547							

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Published OnlineFirst January 26, 2021; DOI: 10.1158/1055-9965.EPI-20-0924

Table 1. Characteristics of the breast cancer population based on data from 67 population-based and hospital-based studies. (Cont'd)

Characteristics	Overall	ER$^+$	ER$^-$	Luminal A–like	Luminal B HER2-negative–like	Luminal B HER2–like	HER2-enriched–like	Triple negative
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)	7,716 (47.9)	11,545 (44.2)	2,813 (42.8)	2,962 (49.4)	1,428 (49.4)	2,925 (45.8)
<18.5 kg/m^2, *n* (%)	1,657 (1.8)	1,103 (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)	5,134 (31.9)	8,939 (34.2)	2,210 (33.6)	1,857 (31.0)	933 (32.3)	2,041 (32.0)
>=30 kg/m^2, *n* (%)	16,435 (18.0)	11,353 (18.1)	2,891 (18.0)	5,228 (20.0)	1,430 (21.8)	1,034 (17.2)	459 (15.9)	1,284 (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)
Missing, *n*	33,481							
Smoking, *n* (%)								
Never	39,512 (59.0)	27,175 (59.3)	7,352 (63.3)	11,767 (60.1)	2,795 (62.4)	2,961 (64.3)	1,581 (68.7)	2,856 (64.0)
Former[g]	17,407 (26.0)	12,082 (26.3)	2,424 (20.9)	4,954 (25.3)	1,093 (24.4)	1,069 (23.2)	387 (16.8)	903 (20.2)
Current[h]	10,073 (15.0)	6,605 (14.4)	1,840 (15.8)	2,850 (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/wk, 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/d, 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/wk, *n* (%)	7,103 (33.3)	4,643 (31.6)	1,043 (31.1)	1,564 (27.1)	305 (24.6)	437 (28.2)	222 (29.1)	418 (31.0)
≥1.8 – <5.5 hours/wk, *n* (%)	7,063 (33.1)	4,679 (31.9)	1,106 (33.0)	1,545 (26.8)	424 (34.2)	491 (31.7)	231 (30.4)	382 (28.3)
≥5.5 hours/wk, *n* (%)	7,154 (33.6)	5,363 (36.5)	1,205 (35.9)	2,656 (46.1)	510 (41.2)	619 (40.1)	308 (40.5)	549 (40.7)
Missing, *n*	100,115							

Note: 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 mo before diagnosis.
[f]At diagnosis or within 6 mo 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 given 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 given for postmenopausal women, while percentages are computed based on all women with non-missing values, including pre-perimenopausal women.

Published OnlineFirst January 26, 2021; DOI: 10.1158/1055-9965.EPI-20-0924

Table 2. Associations between individual risk factors and 10-year all-cause mortality by ER status and intrinsic-like subtype based on the imputed datasets.

Risk factor	Overall *P* HR (95% CI)	ER$^+$ *P* HR (95% CI)	ER$^-$ *P* HR (95% CI)	Luminal A–like *P* HR (95% CI)	Luminal B HER2-negative–like *P* HR (95% CI)	Luminal B HER2-positive-like *P* HR (95% CI)	HER2-enriched–like *P* HR (95% CI)	Triple negative *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 FFTP[a], y	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–<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–<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], y	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]								
	2.4E-01	5.4E-01	1.2E-01	4.7E-01	7.2E-01	4.1E-01	6.7E-01	1.1E-01
Per 6 mo increase	1.02 (0.99–1.04)	1.01 (0.99–1.04)	1.03 (1.00–1.06)	1.01 (0.99–1.04)	1.01 (0.97–1.06)	1.02 (0.99–1.06)	1.01 (0.97–1.05)	1.03 (1.00–1.06)
	7.5E-01	6.2E-01	9.1E-01	5.1E-01	9.1E-01	7.3E-01	9.5E-01	9.0E-01
Ever vs. never	0.97 (0.85–1.10)	0.95 (0.84–1.08)	1.01 (0.84–1.23)	0.93 (0.81–1.08)	0.99 (0.83–1.17)	0.94 (0.76–1.17)	0.99 (0.75–1.31)	1.02 (0.85–1.22)
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–<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–<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–<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–<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–<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–<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)

(Continued on the following page)

Published OnlineFirst January 26, 2021; DOI: 10.1158/1055-9965.EPI-20-0924

Table 2. Associations between individual risk factors and 10-year all-cause mortality by ER status and intrinsic-like subtype based on the imputed datasets. (Cont'd)

Risk factor	Overall *P* HR (95% CI)	ER$^+$ *P* HR (95% CI)	ER$^-$ *P* HR (95% CI)	Luminal A–like *P* HR (95% CI)	Luminal B HER2-negative–like *P* HR (95% CI)	Luminal B HER2-positive-like *P* HR (95% CI)	HER2-enriched–like *P* HR (95% CI)	Triple negative *P* HR (95% CI)
MHT	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)
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/wk	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/d	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/wk	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)

Note: 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 Figs. 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 mo before diagnosis.

[c]At diagnosis or within 6 mo 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.

Published OnlineFirst January 26, 2021; DOI: 10.1158/1055-9965.EPI-20-0924

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.

	All-cause mortality		Breast cancer–specific mortality	
Risk factor	ER status *P*	Intrinsic-like subtype[e] *P*	ER status *P*	Intrinsic-like subtype[e] *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 FFTP[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
MHT[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

Note: 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 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 mo before diagnosis.

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

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

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

mortality [HR (95% CI), 1.53 (1.30–1.80)] for underweight (BMI < 18.5 kg/m^2) compared with normal weight.

Exogenous hormone exposure was associated with reduced all-cause mortality. Compared with never use, ever oral contraceptive 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 with never users [HR (95% CI), 0.58 (0.52–0.65)].

Current cigarette smoking compared with 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 (**Tables 2** and **3**). Some variability was observed in estimates for women who had a recent full-term birth, especially comparing those 0–5 years with ≥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 with that for TN [HR (95% CI), 0.90 (0.65–1.24)]. Risk factors associated with all-cause mortality, such as parity, oral contraceptive 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 Figs. 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 Figs. S17–S22).

Published OnlineFirst January 26, 2021; DOI: 10.1158/1055-9965.EPI-20-0924

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 *P* HR (95% CI)	ER$^+$ *P* HR (95% CI)	ER$^-$ *P* HR (95% CI)	Luminal A–like *P* HR (95% CI)	Luminal B HER2-negative–like *P* HR (95% CI)	Luminal B HER2–like *P* HR (95% CI)	HER2-enriched–like *P* HR (95% CI)	Triple negative *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 FFTP[a], y	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], y	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]								
	4.6E-01	5.4E-01	4.1E-01	4.6E-01	7.2E-01	7.2E-01	6.8E-01	4.8E-01
Per 6 mo increase	1.03 (0.99–1.06)	1.02 (0.99–1.05)	1.03 (1.00–1.07)	1.03 (0.99–1.06)	1.02 (0.97–1.07)	1.02 (0.97–1.07)	1.03 (0.96–1.11)	1.03 (0.99–1.07)
	9.2E-01	9.7E-01	8.7E-01	9.7E-01	9.7E-01	8.7E-01	9.2E-01	7.2E-01
Ever vs. Never	1.02 (0.85–1.22)	1.01 (0.84–1.20)	1.05 (0.83–1.32)	0.99 (0.80–1.23)	0.99 (0.81–1.22)	0.95 (0.71–1.26)	1.04 (0.70–1.55)	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–<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)

(Continued on the following page)

Published OnlineFirst January 26, 2021; DOI: 10.1158/1055-9965.EPI-20-0924

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. (Cont'd)

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)
MHT	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)
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	6.7E-01	7.8E-01	6.7E-01	8.4E-01	8.0E-01	6.1E-01	9.2E-01
	1.02 (0.98–1.07)	1.02 (0.97–1.08)	1.01 (0.97–1.06)	1.03 (0.97–1.09)	1.02 (0.94–1.10)	1.02 (0.95–1.09)	1.05 (0.97–1.13)	1.01 (0.94–1.07)
Alcohol consumption[e], per 10 g/wk	9.0E-01	9.6E-01	8.7E-01	9.8E-01	8.7E-01	8.5E-01	8.8E-01	8.7E-01
	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.98–1.01)	1.00 (0.99–1.01)	1.00 (0.98–1.01)
Cumulative alcohol consumption, per 10 g/d	7.8E-01	7.8E-01	8.7E-01	7.3E-01	9.2E-01	7.2E-01	9.7E-01	8.7E-01
	0.98 (0.91–1.05)	0.97 (0.89–1.07)	0.99 (0.93–1.05)	0.96 (0.87–1.07)	0.99 (0.89–1.10)	0.96 (0.88–1.06)	1.01 (0.90–1.12)	0.99 (0.92–1.06)
Physical activity[e,f], hours/wk	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)

Note: 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 Figs. 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 (TN).

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

[a]Association estimated in parous women.

[b]More than 6 mo before diagnosis.

[c]At diagnosis or within 6 mo 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.

Published OnlineFirst January 26, 2021; DOI: 10.1158/1055-9965.EPI-20-0924

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 with never MHT use [HR (95% CI), 0.61 (0.54–0.69)] and ever use of oral contraceptive compared with never oral contraceptive use [HR (95% CI), 0.91 (0.87–0.96)] were both still associated with all-cause mortality. All-cause mortality was increased in current smokers compared with nonsmokers [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 with 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 Figs. 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 Figures S25 and S26 show the AUC 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 with 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 Fig. S25). For breast cancer–specific mortality, the concordance index was 0.74 for both models (Supplementary Fig. 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 because 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 oral contraceptives 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.

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*
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 FFTP, y		
<20	Ref.	
20–<25	0.90 (0.84–0.96)	1.9E-03
25–<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, y		
≥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 mo	1.02 (1.00–1.04)	6.9E-02
BMI, kg/m^2		
18.5–<25	Ref.	
<18.5	1.31 (0.96–1.77)	5.6E-02
25–<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
MHT		
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
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/wk	1.00 (0.99–1.01)	6.6E-01
Cumulative alcohol consumption, per 10 g/d	1.00 (0.96–1.05)	9.3E-01
Physical activity[d,e], hours/wk		
<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

Note: 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 1,264 cases and 158 deaths from all causes. A comparison between results from imputed data analysis and corresponding complete-case analysis are shown in Supplementary Fig. S23.

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

[a]More than 6 mo before diagnosis.

[b]At diagnosis or within 6 mo 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.

Published OnlineFirst January 26, 2021; DOI: 10.1158/1055-9965.EPI-20-0924

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*
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 FFTP, y		
<20	Ref.	
20–<25	0.90 (0.82–0.99)	2.7E-02
25–<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, y		
≥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 mo	1.02 (1.00–1.05)	7.2E-02
BMI, kg/m^2		
18.5–<25	Ref.	
<18.5	1.10 (0.79–1.53)	5.6E-01
25–<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
MHT		
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
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/wk	1.00 (0.99–1.01)	8.4E-01
Cumulative alcohol consumption, per 10 g/d	0.98 (0.91–1.06)	5.2E-01
Physical activity[d,e], hours/wk		
<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

Note: 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 1,264 cases and 114 deaths from breast cancer. A comparison between results from imputed data analysis and corresponding complete-case analysis are shown in Supplementary Fig. S24.

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

[a]More than 6 mo before diagnosis.

[b]At diagnosis or within 6 mo 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.

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, whereas 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 nonlinear 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 with normal-weight women. The attenuated association between smoking and breast cancer–specific mortality compared with overall mortality could be attributed to the association of smoking with diseases other than breast cancer such as lung cancer and cardiovascular diseases. Comparable with 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 socioeconomic 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, postpartum, or during lactation can be subject to treatment and diagnosis delays, both of which may result in poorer prognosis.

Exposure to exogenous hormones—oral contraceptive and MHT—was observed to be associated with decreased mortality regardless of tumor subtype. Decreased all-cause mortality with ever oral contraceptive use has been inconsistently reported (8, 10, 15, 16) and may be due to differences in timing, duration, and dose of oral contraceptives. 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 because 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 patients with breast cancer available to date. Because of 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. Although 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 this analysis, nine cohort studies provided risk factor information collected more than 1 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, whereas 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 post-diagnosis 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).

Although 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 FFTP, as mentioned previously, as well as exogenous hormone use (oral contraceptives 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.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

A. Morra: Conceptualization, resources, data curation, software, formal analysis, funding acquisition, investigation, methodology, writing–original draft, writing–review and editing. **A.Y. Jung:** Conceptualization, resources, data curation, software, formal analysis, funding acquisition, investigation, methodology, writing–original draft, writing–review and editing. **S. Behrens:** Resources, data curation, funding acquisition, writing–review and editing. **R. Keeman:** Resources, data curation, funding acquisition, writing–review and editing. **T.U. Ahearn:** Resources, funding acquisition, writing–review and editing. **H. Anton-Culver:** Resources, funding acquisition, writing–review and editing. **V. Arndt:** Resources, funding acquisition, writing–review and editing. **A. Augustinsson:** Resources, funding acquisition, writing–review and editing. **P.K. Auvinen:** Resources, funding acquisition, writing–review and editing. **L.E. Beanne Freeman:** Resources, funding acquisition, writing–review and editing. **H. Becher:** Resources, funding acquisition, writing–review and editing. **M.W. Beckmann:** Resources, funding acquisition, writing-review and editing. **C. Blomqvist:** Resources, funding acquisition, writing–review and editing. **S.E. Bojesen:** Resources, funding acquisition, writing–review and editing. **M.K. Bolla:** Resources, data curation, funding acquisition, writing–review and editing. **H. Brenner:** Resources, funding acquisition, writing–review and editing. **I. Briceno:** Resources, funding acquisition, writing–review and editing. **S.Y. Brucker:** Resources, funding acquisition, writing–review and editing. **N.J. Camp:** Resources, funding acquisition, writing–review and editing. **D. Campa:** Resources, funding acquisition, writing–review and editing. **F. Canzian:** Resources, funding acquisition, writing–review and editing. **J.E. Castelao:** Resources, funding acquisition, writing–review and editing. **S.J. Chanock:** Resources, funding acquisition, writing–review and editing. **J.-Y. Choi:** Resources, funding acquisition, writing–review and editing. **C.L. Clarke:** Resources, funding acquisition, writing–review and editing. **F.J. Couch:** Resources, funding acquisition, writing–review and editing. **A. Cox:** Resources, funding acquisition, writing–review and editing. **S.S. Cross:** Resources, funding acquisition, writing–review and editing. **K. Czene:** Resources, funding acquisition, writing–review and

Published OnlineFirst January 26, 2021; DOI: 10.1158/1055-9965.EPI-20-0924

editing. **T. Dörk:** Resources, funding acquisition, writing–review and editing. **A.M. Dunning:** Resources, funding acquisition, writing–review and editing. **M. Dwek:** Resources, funding acquisition, writing–review and editing. **D.F. Easton:** Resources, funding acquisition, writing–review and editing. **D.M. Eccles:** Resources, funding acquisition, writing–review and editing. **K.M. Egan:** Resources, funding acquisition, writing–review and editing. **D.G. Evans:** Resources, funding acquisition, writing–review and editing. **P.A. Fasching:** Resources, funding acquisition, writing–review and editing. **H. Flyger:** Resources, funding acquisition, writing–review and editing. **M. Gago-Dominguez:** Resources, funding acquisition, writing–review and editing. **S.M. Gapstur:** Data curation, funding acquisition, writing–review and editing. **J.A. García-Sáenz:** Resources, funding acquisition, writing–review and editing. **M.M. Gaudet:** Resources, funding acquisition, writing–review and editing. **G.G. Giles:** Resources, funding acquisition, writing–review and editing. **M. Grip:** Resources, funding acquisition, writing–review and editing. **P. Guénel:** Resources, funding acquisition, writing–review and editing. **C.A. Haiman:** Resources, funding acquisition, writing–review and editing. **N. Håkansson:** Resources, funding acquisition, writing–review and editing. **P. Hall:** Resources, funding acquisition, writing–review and editing. **U. Hamann:** Resources, funding acquisition, writing–review and editing. **S.N. Han:** Resources, funding acquisition, writing–review and editing. **S.N. Hart:** Resources, funding acquisition, writing–review and editing. **M. Hartman:** Resources, funding acquisition, writing–review and editing. **J.S. Heyworth:** Resources, funding acquisition, writing–review and editing. **R. Hoppe:** Resources, funding acquisition, writing–review and editing. **J.L. Hopper:** Resources, funding acquisition, writing–review and editing. **D.J. Hunter:** Resources, funding acquisition, writing–review and editing. **H. Ito:** Resources, funding acquisition, writing–review and editing. **A. Jager:** Resources, funding acquisition, writing–review and editing. **M. Jakimovska:** Resources, funding acquisition, writing–review and editing. **A. Jakubowska:** Resources, funding acquisition, writing–review and editing. **W. Janni:** Resources, funding acquisition, writing–review and editing. **R. Kaaks:** Resources, funding acquisition, writing–review and editing. **D. Kang:** Resources, funding acquisition, writing–review and editing. **P. Middha Kapoor:** Resources, funding acquisition, writing–review and editing. **C.M. Kitahara:** Resources, funding acquisition, writing–review and editing. **S. Koutros:** Resources, funding acquisition, writing–review and editing. **P. Kraft:** Resources, funding acquisition, writing–review and editing. **V.N. Kristensen:** Resources, funding acquisition, writing–review and editing. **J.V. Lacey:** Resources, funding acquisition, writing–review and editing. **D. Lambrechts:** Resources, funding acquisition, writing–review and editing. **L. Le Marchand:** Resources, funding acquisition, writing–review and editing. **J. Li:** Resources, funding acquisition, writing–review and editing. **A. Lindblom:** Resources, funding acquisition, writing–review and editing. **J. Lubiński:** Resources, funding acquisition, writing–review and editing. **M. Lush:** Resources, funding acquisition, writing–review and editing. **A. Mannermaa:** Resources, funding acquisition, writing–review and editing. **M. Manoochehri:** Resources, funding acquisition, writing–review and editing. **S. Margolin:** Resources, funding acquisition, writing–review and editing. **S. Mariapun:** Resources, funding acquisition, writing–review and editing. **K. Matsuo:** Resources, funding acquisition, writing–review and editing. **D. Mavroudis:** Resources, funding acquisition, writing–review and editing. **R.L. Milne:** Resources, funding acquisition, writing–review and editing. **T.A. Muranen:** Resources, funding acquisition, writing–review and editing. **W.G. Newman:** Resources, funding acquisition, writing–review and editing. **D.-Y. Noh:** Resources, funding acquisition, writing–review and editing. **B.G. Nordestgaard:** Resources, funding acquisition, writing–review and editing. **N. Obi:** Resources, funding acquisition, writing–review and editing. **A.F. Olshan:** Resources, funding acquisition, writing–review and editing. **H. Olsson:** Resources, funding acquisition, writing–review and editing. **T.-W. Park-Simon:** Resources, funding acquisition, writing–review and editing. **C. Petridis:** Resources, funding acquisition, writing–review and editing. **P.D.P. Pharoah:** Resources, funding acquisition, writing–review and editing. **D. 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Wang:** Resources, data curation, funding acquisition, writing–review and editing. **S.S. Wang:** Resources, funding acquisition, writing–review and editing. **J.A. Williams:** Resources, funding acquisition, writing–review and editing. **R. Winqvist:** Resources, funding acquisition, writing–review and editing. **A. Wolk:** Resources, funding acquisition, writing–review and editing. **A.H. Wu:** Resources, funding acquisition, writing–review and editing. **K.-Y. Yoo:** Resources, funding acquisition, writing–review and editing. **J.-C. Yu:** Resources, funding acquisition, writing–review and editing. **W. Zheng:** Resources, funding acquisition, writing–review and editing. **A. Ziogas:** Resources, funding acquisition, writing–review and editing. **X.R. Yang:** Resources, funding acquisition, writing–review and editing. **A.H. Eliassen:** Resources, funding acquisition, writing–review and editing. **M.D. Holmes:** Resources, funding acquisition, writing–review and editing. **M. García-Closas:** Resources, funding acquisition, writing–review and editing. **S.H. Teo:** Resources, funding acquisition, writing–review and editing. **M.K. Schmidt:** Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, investigation, methodology, writing–original draft, writing–review and editing. **J. Chang-Claude:** Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, investigation, methodology, writing–original draft, writing–review and editing.

Acknowledgments

We thank all the individuals who took part in these studies and all the researchers, clinicians, technicians, and administrative staff who have enabled this work to be carried out. This work was supported by the following funding agencies:

The Breast Cancer Association Consortium (all authors, directly or indirectly through having samples genotyped on the iCOGS and/or OncoArray and/or having their data incorporated in the BCAC database) is funded by Cancer Research UK (C1287/A16563, C1287/A10118), the European Union's Horizon 2020 Research and Innovation Programme (grant numbers 634935 and 633784 for BRIDGES and B-CAST, respectively), and by the European Community's Seventh Framework Programme under grant agreement number 223175 (grant number HEALTH-F2–2009–223175; COGS). The EU Horizon 2020 Research and Innovation Programme funding source had no role in study design, data collection, data analysis, data interpretation or writing of the report.

The Australian Breast Cancer Family Study (ABCFS; principal investigators: J.L. Hopper, M.C. Southey) was supported by grant UM1 CA164920 from the NCI (Rockville, MD). The content of this manuscript does not necessarily reflect the views or policies of the NCI or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government or the BCFR. The ABCFS was also supported by the National Health and Medical Research Council of Australia, the New South Wales Cancer Council, the Victorian Health Promotion Foundation (Australia), and the Victorian Breast Cancer Research Consortium. J.L. Hopper is a National Health and Medical Research Council (NHMRC) senior principal research fellow. M.C. Southey is a NHMRC Senior Research Fellow. ABCFS thank Maggie Angelakos, Judi Maskiell, and Gillian Dite. The ABCS study (principal investigator: M.K. Schmidt) was supported by the Dutch Cancer Society (grants NKI 2007–3839; 2009 4363). ABCS thanks the Blood bank Sanquin, the Netherlands.

The Australian Breast Cancer Tissue Bank (ABCTB) Investigators: Christine Clarke, Deborah Marsh, Rodney Scott, Robert Baxter, Desmond Yip, Jane Carpenter, Alison Davis, Nirmala Pathmanathan, Peter Simpson, J. Dinny Graham, Mythily Sachchithananthan. Samples are made available to researchers on a nonexclusive basis. The ABCTB (principal investigator: C.L. Clarke) was supported by the National Health and Medical Research Council of Australia, The Cancer Institute NSW, and the National Breast Cancer Foundation.

The AHS study (principal investigator: S. Koutros) is supported by the intramural research program of the NIH, NCI (grant number Z01-CP010119), and the National Institute of Environmental Health Sciences (grant number Z01-ES049030).

The work of the BBCC (principal investigator: P.A. Fasching) was partly funded by ELAN-Fond of the University Hospital of Erlangen.

The BCEES (principal investigators: J. Stone, L. Fritschi) was funded by the National Health and Medical Research Council, Australia and the Cancer Council Western Australia. BCEES thanks Allyson Thomson, Christobel Saunders, Terry Slevin, BreastScreen Western Australia, Elizabeth Wylie, and Rachel Lloyd.

The BCINIS study (principal investigator: G. Rennert) is supported, in part, by the Breast Cancer Research Foundation (BCRF). The BCINIS study would not have been possible without the contributions of Dr. K. Landsman, Dr. N. Gronich, Dr. A. Flugelman, Dr. W. Saliba, Dr. F. Lejbkowicz, Dr. E. Liani, Dr. I. Cohen, Dr. S. Kalet, Dr. V. Friedman, Dr. O. Barnet of the NICCC in Haifa, Israel, and all the contributing family medicine, surgery, pathology, and oncology teams in all medical institutes in Northern Israel.

BIGGS thanks Niall McInerney, Gabrielle Colleran, Andrew Rowan, Angela Jones. For BIGGS, E.J. Sawyer is supported by NIHR Comprehensive Biomedical Research Centre, Guy's & St. Thomas' NHS Foundation Trust in partnership with King's College London, United Kingdom. I. Tomlinson is supported by the Oxford Biomedical Research Centre.

The BREast Oncology GAlician Network (BREOGAN) study would not have been possible without the contributions of the following: Manuela Gago-Dominguez, Jose Esteban Castelao, Angel Carracedo, Victor Muñoz Garzón, Alejandro Novo Domínguez, Maria Elena Martinez, Sara Miranda Ponte, Carmen Redondo Marey, Maite Peña Fernández, Manuel Enguix Castelo, Maria Torres, Manuel Calaza (BREOGAN), José Antúnez, Máximo Fraga, and the staff of the Department of Pathology and Biobank of the University Hospital Complex of Santiago-CHUS, Instituto de Investigación Sanitaria de Santiago, IDIS, Xerencia de Xestion Integrada de Santiago-SERGAS; Joaquín González-Carreró and the staff of the Department of Pathology and Biobank of University Hospital Complex of Vigo, Instituto de Investigacion Biomedica Galicia Sur, SERGAS, Vigo, Spain. The BREOGAN (principal investigators: J.E. Castelao, M. Gago-Dominguez) is funded by Acción Estratégica de Salud del Instituto de Salud Carlos III FIS PI12/02125/Cofinanciado FEDER, PI17/00918/Cofinanciado FEDER; Acción Estratégica de Salud del Instituto de Salud Carlos III FIS Intrasalud (PI13/01136); Programa Grupos Emergentes, Cancer Genetics Unit, Instituto de Investigacion Biomedica Galicia Sur. Xerencia de Xestion Integrada de Vigo-SERGAS, Instituto de Salud Carlos III, Spain; Grant 10CSA012E, Consellería de Industria Programa Sectorial de Investigación Aplicada, PEME I + D e I + D Suma del Plan Gallego de Investigación, Desarrollo e Innovación Tecnológica de la Consellería de Industria de la Xunta de Galicia, Spain (grant EC11–192); Fomento de la Investigación Clínica Independiente, Ministerio de Sanidad, Servicios Sociales e Igualdad, Spain; and Grant FEDER-Innterconecta. Ministerio de Economia y Competitividad, Xunta de Galicia, Spain.

BSUCH thanks Peter Bugert, Medical Faculty Mannheim, Germany. The BSUCH study (principal investigator: B. Burwinkel) was supported by the Dietmar-Hopp Foundation, the Helmholtz Society, and the German Cancer Research Center (DKFZ).

CCGP thanks Styliani Apostolaki, Anna Margiolaki, Georgios Nintos, Maria Perraki, Georgia Saloustrou, Georgia Sevastaki, Konstantinos Pompodakis. CCGP (principal investigator: E. Saloustros) is supported by funding from the University of Crete.

The CECILE study (principal investigator: P. Guénel) was supported by Fondation de France, Institut National du Cancer (INCa), Ligue Nationale contre le Cancer, Agence Nationale de Sécurité Sanitaire, de l'Alimentation, de l'Environnement et du Travail (ANSES), Agence Nationale de la Recherche (ANR).

The CGPS thanks staff and participants of the Copenhagen General Population Study. For the excellent technical assistance: Dorthe Uldall Andersen, Maria Birna Arnadottir, Anne Bank, Dorthe Kjeldgård Hansen. The Danish Cancer Biobank is acknowledged for providing infrastructure for the collection of blood samples for the cases. The CGPS (principal investigator: S.E. Bojesen) was supported by the Chief Physician Johan Boserup and Lise Boserup Fund, the Danish Medical Research Council, and Herlev and Gentofte Hospital.

COLBCCC thanks all patients, the physicians Justo G. Olaya, Mauricio Tawil, Lilian Torregrosa, Elias Quintero, Sebastian Quintero, Claudia Ramírez, José J. Caicedo, and Jose F. Robledo, and the technician Michael Gilbert for their contributions and commitment to this study. COLBCCC (principal investigator: U. Hamann) is supported by the German Cancer Research Center (DKFZ), Heidelberg, Germany.

D. Torres was, in part, supported by a postdoctoral fellowship from the Alexander von Humboldt Foundation. Investigators from the CPS-II cohort thank the participants and Study Management Group for their invaluable contributions to this research. They also acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention National Program of Cancer Registries, as well as cancer registries supported by the National Cancer Institute Surveillance Epidemiology and End Results program. The American Cancer Society funds the creation, maintenance, and updating of the CPS-II cohort (principal investigators: S.M. Gapstur, M.M. Gaudet). The authors would like to thank the California Teachers Study Steering Committee that is responsible for the formation and maintenance of the Study within which this research was conducted. A full list of California Teachers Study team members is available at https://www.calteachersstudy.org/team. The California Teachers Study (principal investigator: J.V. Lacey) and the research reported in this publication were supported by the NCI of the NIH under award numbers U01-CA199277; P30-CA033572; P30-CA023100; UM1-CA164917; and R01-CA077398. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NCI or the NIH. The collection of cancer incidence data used in the California Teachers Study (principal investigator: J.V. Lacey) was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; Centers for Disease Control and Prevention's National Program of Cancer Registries, under cooperative agreement 5NU58DP006344; NCI's Surveillance, Epidemiology and End Results Program under contract HHSN261201800032I awarded to the University of California, San Francisco; contract HHSN261201800015I awarded to the University of Southern California; and contract HHSN261201800009I awarded to the Public Health Institute. The opinions, findings, and conclusions expressed herein are those of the author(s) and do not necessarily reflect the official views of the State of California, Department of Public Health, the NCI, the NIH, the Centers for Disease Control and Prevention or their Contractors and Subcontractors, or the Regents of the University of California, or any of its programs.

DIETCOMPLYF thanks the patients, nurses and clinical staff involved in the study. The University of Westminster curates the DietCompLyf database (principal investigator: M. Dwek) funded by Against Breast Cancer Registered Charity no. 1121258 and the NCRN. We thank the participants and the investigators of EPIC (European Prospective Investigation into Cancer and Nutrition). The coordination of EPIC (principal investigator: R. Kaaks) is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by: Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center (DKFZ), Federal Ministry of Education and Research (BMBF, Germany); the Hellenic Health Foundation, the Stavros Niarchos Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (the Netherlands); Health Research Fund (FIS), PI13/00061 to Granada, PI13/01162 to EPIC-Murcia, Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, ISCIII RETIC (RD06/0020) (Spain); Cancer Research UK (14136 to EPIC-Norfolk; C570/A16491 and C8221/A19170 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk, MR/M012190/1 to EPIC-Oxford; United Kingdom).

The ESTHER study thanks Hartwig Ziegler, Sonja Wolf, Volker Hermann, Christa Stegmaier, Katja Butterbach. The ESTHER study (principal investigator: H. Brenner) was supported by a grant from the Baden Württemberg Ministry of Science, Research and Arts. Additional cases were recruited in the context of the VERDI study, which was supported by a grant from the German Cancer Aid (Deutsche Krebshilfe).

The GENICA Network: Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, and University of Tübingen, Germany (Hiltrud Brauch, Wing-Yee Lo), Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany (Yon-Dschun Ko, Christian Baisch), Institute of Pathology, University of Bonn, Germany (Hans-Peter Fischer), Molecular Genetics of Breast Cancer, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany (UH), Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, Germany (Thomas Brüning, Beate Pesch, Sylvia Rabstein, Anne Lotz); and Institute of Occupational Medicine and Maritime Medicine, University Medical Center Hamburg-Eppendorf, Germany (Volker Harth). The GENICA (principal investigator: H. Brauch) was funded by the Federal Ministry of Education and Research (BMBF) Germany grants 01KW9975/5, 01KW9976/8, 01KW9977/0 and 01KW0114, the Robert Bosch Foundation, Stuttgart, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum,

as well as the Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany.

The GESBC (principal investigator: J. Chang-Claude) was supported by the Deutsche Krebshilfe e. V. (70492) and the German Cancer Research Center (DKFZ).

HABCS would like to thank Peter Schürmann, Natalia Bogdanova, Nikki Adrian Krentel, Regina Meier, Frank Papendorf, Michael Bremer, Johann H. Karstens, Hans Christiansen, and Peter Hillemanns for their contributions to this study. The HABCS (principal investigator: T. Dörk) was supported by the Claudia von Schilling Foundation for Breast Cancer Research, by the Lower Saxonian Cancer Society, and by the Rudolf Bartling Foundation. HEBCS would like to thank Heli Nevanlinna, Kristiina Aittomäki, Karl von Smitten, and Kirsi Aaltonen for their contribution for this study.

The HEBCS (principal investigator: H. Nevanlinna) was financially supported by the Helsinki University Hospital Research Fund, the Finnish Cancer Society, and the Sigrid Juselius Foundation.

The HERPACC (principal investigator: K. Matsuo) was supported by MEXT Kakenhi (no. 170150181 and 26253041) from the Ministry of Education, Science, Sports, Culture and Technology of Japan, by a Grant-in-Aid for the Third Term Comprehensive 10-Year Strategy for Cancer Control from Ministry Health, Labour and Welfare of Japan, by Health and Labour Sciences Research Grants for Research on Applying Health Technology from Ministry Health, Labour and Welfare of Japan, by National Cancer Center Research and Development Fund, and "Practical Research for Innovative Cancer Control (15ck0106177h0001)" from Japan Agency for Medical Research and development, AMED, and Cancer Bio Bank Aichi.

ICICLE thanks Kelly Kohut, Michele Caneppele, Maria Troy. ICICLE (principal investigator: E.J. Sawyer) was supported by Breast Cancer Now, CRUK and Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London.

Financial support for KARBAC (principal investigators: A. Lindblom, S. Margolin) was provided through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet, the Swedish Cancer Society, The Gustav V Jubilee foundation and Bert von Kantzows foundation.

KARMA and SASBAC thank the Swedish Medical Research Counsel. The KARMA study (principal investigators: K. Czene, P. Hall) was supported by Märit and Hans Rausings Initiative Against Breast Cancer.

The KBCP (principal investigator: A. Mannermaa) was financially supported by the special Government Funding (EVO) of Kuopio University Hospital grants, Cancer Fund of North Savo, the Finnish Cancer Organizations, and by the strategic funding of the University of Eastern Finland.

LAABC thanks all the study participants and the entire data collection team, especially Annie Fung and June Yashiki. LAABC (principal investigator: A.H. Wu) is supported by grants (1RB-0287, 3PB-0102, 5PB-0018, 10PB-0098) from the California Breast Cancer Research Program. Incident breast cancer cases were collected by the USC Cancer Surveillance Program (CSP) which is supported under subcontract by the California Department of Health. The CSP is also part of the National Cancer Institute's Division of Cancer Prevention and Control Surveillance, Epidemiology, and End Results Program, under contract number N01CN25403.

LMBC thanks Gilian Peuteman, Thomas Van Brussel, EvyVanderheyden, and Kathleen Corthouts. LMBC (principal investigator: D. Lambrechts) is supported by the "Stichting tegen Kanker." D. Lambrechts is supported by the FWO.

MABCS thanks Snezhana Smichkoska, Emilija Lazarova (University Clinic of Radiotherapy and Oncology), Katerina Kubelka-Sabit, Mitko Karadjozov (Adzibadem-Sistina Hospital), Andrej Arsovski, and Liljana Stojanovska (Re-Medika Hospital) for their contributions and commitment to this study. The MABCS study (to D. Plaseska-Karanfilska, M. Jakimovska) is funded by the Research Centre for Genetic Engineering and Biotechnology "Georgi D. Efremov," MASA.

MARIE thanks Petra Seibold, Dieter Flesch-Janys, Judith Heinz, Alina Vrieling, Ursula Eilber, Muhabbet Celik, Til Olchers, and Stefan Nickels. The MARIE study (principal investigator: J. Chang-Claude) was supported by the Deutsche Krebshilfe e.V. (70–2892-BR I, 106332, 108253, 108419, 110826, 110828), the Hamburg Cancer Society, the German Cancer Research Center (DKFZ) and the Federal Ministry of Education and Research (BMBF) Germany (01KH0402 and 01ER1306).

The MCBCS (principal investigator: F.J. Couch) was supported by the NIH grants CA192393, CA116167, CA176785 an NIH Specialized Program of Research Excellence (SPORE) in Breast Cancer (CA116201), and the Breast Cancer Research Foundation and a generous gift from the David F. and Margaret T. Grohne Family Foundation.

The Melbourne Collaborative Cohort Study (MCCS) was made possible by the contribution of many people, including the original investigators, the teams that recruited the participants and continue working on follow-up, and the many thousands of Melbourne residents who continue to participate in the study. The MCCS cohort recruitment was funded by VicHealth and Cancer Council Victoria (principal investigators: G.G. Giles and R.L. Milne). The MCCS was further augmented by Australian National Health and Medical Research Council grants 209057, 396414, and 1074383 and by infrastructure provided by Cancer Council Victoria (principal investigators: G.G. Giles and R.L. Milne). Cases and their vital status were ascertained through the Victorian Cancer Registry and the Australian Institute of Health and Welfare, including the National Death Index and the Australian Cancer Database.

The MEC (principal investigator: C.A. Haiman) was supported by NIH grants CA63464, CA54281, CA098758, CA132839 and CA164973. The MISS study (principal investigator: H. Olsson) is supported by funding from ERC-2011–294576 Advanced grant, Swedish Cancer Society, Swedish Research Council, Local hospital funds, Berta Kamprad Foundation, Gunnar Nilsson.

We thank the coordinators, the research staff and especially the MMHS participants for their continued collaboration on research studies in breast cancer. The MMHS study (principal investigator: C.M. Vachon) was supported by NIH grants CA97396, CA128931, CA116201, CA140286 and CA177150.

MYBRCA thanks study participants and research staff (particularly Patsy Ng, Nurhidayu Hassan, Yoon Sook-Yee, Daphne Lee, Lee Sheau Yee, Phuah Sze Yee and Norhashimah Hassan) for their contributions and commitment to this study. MYBRCA (principal investigator: S.H. Teo) is funded by research grants from the Malaysian Ministry of Higher Education (UM.C/HlR/MOHE/06) and Cancer Research Malaysia.

The following are NBCS Collaborators: Kristine K. Sahlberg (PhD), Lars Ottestad (MD), Rolf Kåresen (Prof. Em.), Anne-Lise Børresen-Dale (Prof. Em.), Dr. Ellen Schlichting (MD), Marit Muri Holmen (MD), Toril Sauer (MD), Vilde Haakensen (MD), Olav Engebråten (MD), Bjørn Naume (MD), Alexander Fosså (MD), Cecile E. Kiserud (MD), Kristin V. Reinertsen (MD), Åslaug Helland (MD), Margit Riis (MD), Jürgen Geisler (MD), OSBREAC and Grethe I. Grenaker Alnæs (MSc). The NBCS (principal investigator: V.N. Kristensen) has received funding from the K.G. Jebsen Centre for Breast Cancer Research; the Research Council of Norway grant 193387/V50 (to A.-L. Børresen-Dale and V.N. Kristensen) and grant 193387/H10 (to A.-L. Børresen-Dale and V.N. Kristensen), South Eastern Norway Health Authority (grant 39346 to A.-L. Børresen-Dale) and the Norwegian Cancer Society (to A.-L. Børresen-Dale and V.N. Kristensen).

The Carolina Breast Cancer Study (NCBCS, principal investigator: M.A. Troester) was funded by Komen Foundation, the NCI (P50 CA058223, U54 CA156733, U01 CA179715), and the North Carolina University Cancer Research Fund.

For NHS and NHS2, the study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. We would like to thank the participants and staff of the NHS and NHS2 for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data. The NHS (principal investigator: H.A. Eliassen) was supported by NIH grants P01 CA87969, UM1 CA186107, and U19 CA148065. The NHS2 (principal investigator: W. Willett) was supported by NIH grants U01 CA176726 and U19 CA148065.

OBCS thanks Katri Pylkäs, Arja Jukkola, Saila Kauppila, Meeri Otsukka, Leena Keskitalo, and Kari Mononen for their contributions to this study. The OBCS (principal investigator: R. Winqvist) was supported by research grants from the Finnish Cancer Foundation, the Academy of Finland (grant number 250083, 122715 and Center of Excellence grant number 251314), the Finnish Cancer Foundation, the Sigrid Juselius Foundation, the University of Oulu, the University of Oulu Support Foundation and the special Governmental EVO funds for Oulu University Hospital-based research activities.

ORIGO thanks E. Krol-Warmerdam, and J. Blom for patient accrual, administering questionnaires, and managing clinical information. The LUMC survival data were retrieved from the Leiden hospital–based cancer registry system (ONCDOC) with the help of Dr. J. Molenaar. The ORIGO study (principal investigator: P. Devilee) was supported by the Dutch Cancer Society (RUL 1997–1505) and the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL CP16).

PBCS thanks Louise Brinton, Mark Sherman, Neonila Szeszenia-Dabrowska, Beata Peplonska, Witold Zatonski, Pei Chao, Michael Stagner. The PBCS (principal investigator: M. García-Closas) was funded by Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services.

Genotyping for PLCO (principal investigator: M. García-Closas) was supported by the Intramural Research Program of the NIH, NCI, Division of Cancer Epidemiology and Genetics. The PLCO (principal investigator: M. García-Closas) is supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics and supported by contracts from the Division of Cancer Prevention, NCI, NIH.

The ethical approval for the POSH study is MREC/00/6/69, UKCRN ID: 1137. We thank staff in the Experimental Cancer Medicine Centre (ECMC) supported Faculty of Medicine Tissue Bank and the Faculty of Medicine DNA Banking resource.

The POSH study (principal investigators: W. Tapper, D.M. Eccles) is funded by Cancer Research UK (grants C1275/A11699, C1275/C22524, C1275/A19187, C1275/A15956 and Breast Cancer Campaign 2010PR62, 2013PR044. PREFACE thanks Sonja Oeser and Silke Landrith. PROCAS thanks NIHR for funding.

SBCS thanks Sue Higham, Helen Cramp, Dan Connley, Ian Brock, Sabapathy Balasubramanian and Malcolm W.R. Reed.

PROCAS (principal investigator: D.G. Evans) is funded by NIHR grant PGfAR 0707–10031. D.G. Evans is supported by the all Manchester NIHR Biomedical Research Centre (IS-BRC-1215–20007).

The SASBAC study (principal investigators: P. Hall, K. Czene) was supported by funding from the Agency for Science, Technology and Research of Singapore (A*STAR), the US NIH, and the Susan G. Komen Breast Cancer Foundation. The SBCGS (principal investigators: W. Zheng, X.-O. Shu) was supported primarily by NIH grants R01CA64277, R01CA148667, UMCA182910, and R37CA70867. Biological sample preparation was conducted the Survey and Biospecimen Shared Resource, which is supported by P30 CA68485. The scientific development and funding of this project were, in part, supported by the Genetic Associations and Mechanisms in Oncology (GAME-ON) Network U19 CA148065.

The SBCS (principal investigator: A. Cox) was supported by Sheffield Experimental Cancer Medicine Centre and Breast Cancer Now Tissue Bank. We thank the SEARCH and EPIC teams.

SEARCH (principal investigator: P.D.P. Pharoah) is funded by Cancer Research UK [C490/A10124, C490/A16561] and supported by the UK National Institute for Health Research Biomedical Research Centre at the University of Cambridge. The University of Cambridge has received salary support for P.D.P. Pharoah from the NHS in the East of England through the Clinical Academic Reserve.

SEBCS (principal investigators: D. Kang, J.-Y. Choi) was supported by the BRL (Basic Research Laboratory) program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (2012–0000347). SGBCC thanks the participants and all research coordinators for their excellent help with recruitment, data and sample collection.

SGBCC (principal investigators: M. Hartman, J. Li) is funded by the National Research Foundation Singapore, NUS start-up Grant, National University Cancer Institute Singapore (NCIS) Centre Grant, Breast Cancer Prevention Programme, Asian Breast Cancer Research Fund and the NMRC Clinician Scientist Award (SI Category). Additional controls were recruited by the Singapore Consortium of Cohort Studies-Multi-ethnic cohort (SCCS-MEC), which was funded by the Biomedical Research Council, grant number: 05/1/21/19/425.

SKKDKFZS thanks all study participants, clinicians, family doctors, researchers and technicians for their contributions and commitment to this study. SKKDKFZS (principal investigator: U. Hamann) is supported by the DKFZ.

The SMC (principal investigator: A. Wolk) is funded by the Swedish Cancer Foundation and the Swedish Research Council (VR 2017–00644) grant for the Swedish Infrastructure for Medical Population-based Life-course Environmental Research (SIMPLER).

We thank the SUCCESS Study teams in Munich, Duessldorf, Erlangen, and Ulm.

SZBCS thanks Ewa Putresza. The SZBCS (principal investigator: A. Jakubowska) was supported by grant PBZ_KBN_122/P05/2004 and the program of the Minister of Science and Higher Education under the name "Regional Initiative of Excellence" in 2019–2022 project number 002/RID/2018/19 amount of financing 12 000 000 PLN.

The TWBCS (principal investigator: C.-Y. Shen) is supported by the Taiwan Biobank project of the Institute of Biomedical Sciences, Academia Sinica, Taiwan.

UBCS thanks all study participants, the ascertainment, laboratory and research informatics teams at Huntsman Cancer Institute and Intermountain Healthcare, and Stacey Knight, Melissa Cessna and Kerry Rowe for their important contributions to this study. Ascertainment and data collection for the UBCS (principal investigator: N. J. Camp) is supported by funding from NCI grants R01 CA163353 (to N.J. Camp) and the Women's Cancer Center at the Huntsman Cancer Institute (HCI), which is funded in part by the Huntsman Cancer Foundation. Data collection is also made possible by the Utah Population Database (UPDB), Intermountain Healthcare, and the Utah Cancer Registry (UCR). Support for the UPDB is provided by the University of Utah, HCI, and the Comprehensive Cancer Center Support grant NCI P30 CA42014. The UCR is funded by the NCI's SEER Program (contract no. HHSN261201800016I), with additional support from the US Center for Disease Control and Prevention's National Program of Cancer Registries (Cooperative Agreement No. NU58DP0063200), and the University of Utah and Huntsman Cancer Foundation.

UCIBCS thanks Irene Masunaka. The UCIBCS component of this research (principal investigator: H. Anton-Culver) was supported by the NIH (CA58860, CA92044) and the Lon V Smith Foundation (LVS39420).

The US3SS study (principal investigator: M. García-Closas) was supported by Massachusetts (to K.M. Egan, R01CA47305), Wisconsin (to P.A. Newcomb, R01 CA47147), and New Hampshire (to L.Titus-E., R01CA69664) centers, and Intramural Research Funds of the NCI, Department of Health and Human Services.

The USRT Study (principal investigators: C.M. Kitahara, M. García-Closas) was funded by Intramural Research Funds of the NCI, Department of Health and Human Services.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received June 17, 2020; revised August 31, 2020; accepted January 8, 2021; published first January 26, 2021.

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