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ABSTRACT

Background: Breast cancer risk remains higher in high-income compared with low-income countries. However, it is unclear to what degree metabolic factors influence breast cancer development in women 30 years after immigration from low- to a high-incidence country.

Methods: Using Cox regression models, we studied the association between pre-diagnostic metabolic factors and breast cancer development, and whether this association varied by ethnicity among 13,802 women participating in the population-based Oslo Ethnic Breast Cancer Study. Ethnic background was assessed and pre-diagnostic metabolic factors (body mass index, waist:hip ratio, serum lipids and blood pressure) were measured. A total of 557 women developed invasive breast cancer, and these women were followed for an additional 7.7 years.

Results: Among women with an unfavorable metabolic profile, women from south Asia, compared with western European women, had a 2.3 times higher breast cancer risk (HR 2.30, 95% CI 1.18–4.49). Compared with the western European women, the ethnic minority women were more likely to present with triple-negative breast cancer (TNBC) (OR 2.11, 95% CI 0.97–4.61), and less likely to complete all courses of planned taxane treatment (OR 0.26, 95% CI 0.08–0.82). Among TNBC women, above-median triglycerides:HDL-cholesterol (>0.73) levels, compared with below-median triglycerides:HDL-cholesterol (≤0.73) levels, was associated with 2.9 times higher overall mortality (HR 2.88, 95% CI 1.02–8.11).

Conclusions: Our results support the importance of metabolic factors when balancing breast cancer prevention and disease management among all women, and in particular among non-western women migrating from a breast cancer low-incidence to a high-incidence country.

Introduction

It is well known that women who move from a country with low breast cancer incidence to a high-incidence country increase their breast cancer risk, and the rates grow with the number of years lived in the present country [1,2]. However, to what degree modifiable metabolic factors, i.e., body composition and blood pressure (BP), affect breast cancer risk among immigrant women moving to Europe compared with western European women, remain equivocal. Immigration to Norway from countries outside Europe, and in particular from Asia, started in the 1970s [3]. In parallel to this rising immigration, an obesity epidemic evolved in Norway [4], also observed among certain immigrant communities [5]. Furthermore, a stronger association between body mass index (BMI in kg/m²) and risk of type 2 diabetes has been shown in immigrant women to Norway compared with the majority population [6].

Biological mechanisms linking obesity to breast cancer development, involve among others; insulin resistance, oxidative stress and a low-grade chronic inflammation [7,8]. Despite that obesity and several lifestyle-related diseases are more common among immigrant women in Norway, a life-long breast cancer risk was recently observed to be lower in the non-western immigrant women compared with the ethnic Norwegian women [9]. However, a meta-analysis demonstrated that obesity and breast cancer risk may vary according to ethnicity [10], suggesting that obesity affects individuals of different ethnicities disproportionately to their risk for breast cancer.

Women who have migrated from a country with low to one with high breast cancer incidence, often present with a more advanced breast cancer stage at diagnosis [11,12], and women with low socioeconomic status may have poorer breast cancer survival [13]. Thus, we question whether breast cancer patients, with different ethnicity, receive optimal

breast cancer treatment in a country with a universal health-care system and national breast cancer treatment guidelines.

Implying an elevated vulnerability to lifestyle-related diseases exists among non-western immigrant women [6], we hypothesized that an unfavorable metabolic profile may influence breast cancer development differently in non-western immigrant women to Norway compared with western European women. Hence, using pre-diagnostic metabolic factors (BMI, waist:hip ratio [WHR], serum lipids and BP), we studied the association between ethnicity and breast cancer risk, tumor characteristics and treatment, and whether these metabolic factors influence mortality.

Methods

Between 2000 and 2003, women were invited to participate in three population-based cohort studies in Oslo [6,14,15]. Although different population subgroups were targeted, the same protocol was used for all three studies. Of those invited, 15,310 women, aged 15–75 years, participated (attendance rate 42–48%).

Questionnaires

Assessment of lifestyle and reproductive factors

The questionnaires were translated into 11 languages, and included questions about education, current income-generating work, reproductive factors (age at menarche, number of children), use of menopausal hormone therapy (MHT), medication use, cigarette smoking, alcohol use and physical activity.

We dichotomized the following variables: education (<14 years: lower education; ≥14 years: higher education), current income-generating work (yes, no), MHT (never, pervious/current), cholesterol-lowering and BP medications (current use, no/previous use), cigarette smoking (current smoker, none/previous smoker), alcohol intake (0–1 time/month, >1 time/month) and physical activity (moderate: ≥3 h of light exercise and/or ≥1 h of heavy exercise per week; sedentary: <3 h of light exercise and <1 h of heavy exercise).

Assessment of ethnicity

Ethnicity was defined by the participant's country of birth [16]. If information was missing on a participant's birth country, we used the mother's birth country. Women from Norway and immigrants of European descent (Nordic countries, western Europe, Australia and North America) are referred to as western European women, representing the reference population. All other women encompass non-western immigrants migrating from countries with historically lower breast cancer incidence, and are referred to as ethnic minority women [12,17]. To study the heterogeneity of the ethnic minority women, we classified three major ethnic groups: (1) south Asia (Pakistan, India and Sri Lanka), (2) Middle East and north Africa, and (3) all other ethnic minority groups (eastern Europe, east Asia, sub-Saharan Africa and Central/South America).

Assessment of anthropometric factors, BP and serum samples

All the procedures were performed by experienced and trained personnel. Body weight (kg) and height (cm) were measured using electronic height and weight scales with the participants wearing light clothing without shoes. Waist and hip circumferences were measured according to a standard protocol [18].

Heart rate, systolic and diastolic BPs (mmHg) were measured by an automatic device (DINAMAP, Criticon, Tampa, FL, USA), and mean values of the second and third measurements were used [14].

Non-fasting serum total cholesterol, serum high-density lipoprotein-cholesterol (HDL-C) and serum triglycerides (TGs) were measured directly using an enzymatic method (Hitachi 917 autoanalyzer, Roche Diagnostic, Switzerland), and the time since the last meal was recorded [19]. The laboratory investigations were performed by the Department of Clinical Chemistry, Ullevål University Hospital, Norway.

Identification of breast cancer cases during follow-up

Breast cancer cases diagnosed during follow-up were identified through linkage to the Cancer Registry of Norway by the unique national 11-digit identification number [20]. We obtained information on death and emigration from the Cause of Death Registry and the National Population Registry, respectively. We excluded women with a previous history of breast cancer ($n = 29$), women with missing information on ethnicity ($n = 269$), women aged <20 years at study enrollment ($n = 24$), women with missing information on BMI, WHR, BP, and TG and HDL-C levels ($n = 88$), and those with missing information on reproductive factors ($n = 1,088$) (Supplementary Figure 1). Thus, 13,802 women were included in the final study population.

The participants were followed from the date of study enrollment until the end of follow-up (31 December 2018), date of breast cancer diagnosis, emigration or death, whichever occurred first. A total of 557 women were diagnosed with invasive breast cancer during follow-up (Supplementary Figure 1).

Available histopathological and clinical information from each patient's medical chart was abstracted and cross-checked by two trained oncologists (T.L. and H.F.). The information assessed included TNM classification (tumor size, nodal involvement, metastases), histological type and grade (1–3), estrogen/progesterone receptor (ER/PgR) and human epidermal growth factor receptor-2 (HER2) status, and proliferation marker (Ki-67 hot spot). A subset of the breast cancer cases ($n = 440$) with complete information on receptor status was categorized into three molecularly defined subgroups: (1) hormone receptor positive – patients with ER-positive (with or without PgR-positive) and HER2-negative status; (2) HER2 positive – all patients with HER2 overexpression; and

(3) triple-negative breast cancer (TNBC) – HER2-, ER- and PgR-negative status.

Detailed information about treatment was assessed (treatment intention, surgery, chemotherapy, endocrine therapy, and radiotherapy). Completion of planned chemotherapy courses was defined as follows: taxane treatment: 12 weekly paclitaxel courses or 4 docetaxel courses; anthracycline treatment: six courses of FEC-60 (5-fluorouracil, epirubicin, cyclophosphamide), four or six courses of FEC-100 or four courses of EC-90 (epirubicin, cyclophosphamide), according to the change in treatment guidelines through follow-up [21]. Completion of planned trastuzumab treatment (17 cycles) was not studied due to the low number of HER2-positive breast cancer cases.

Follow-up after breast cancer diagnosis was calculated from the date of the diagnosis to the date of death, emigration or end of follow-up.

Statistical methods

Metabolic profile included the following factors that were dichotomized by the median: BMI ($\leq$24.6 and >24.6 kg/m^2), WHR ($\leq$0.79 and >0.79), TG:HDL-C ($\leq$0.73 and >0.73) [22], and BP (mmHg) defined as systolic BP + diastolic BP divided by 2 ($\leq$96.5 and >96.5 mmHg) [23]. For each metabolic factor, a value above the median was defined as an unfavorable (metabolic) factor. To study the potential effect of the four unfavorable metabolic factors combined, we defined three metabolic profiles based on the number of unfavorable metabolic factors: profile 1: 0–2 unfavorable factors; profile 2: 3 unfavorable factors; and profile 3: 4 unfavorable factors.

We used Cox proportional hazard regression to study the association between ethnicity and invasive breast cancer risk in total and stratified by specific pre-diagnostic metabolic factors/profiles among all participating women, and between metabolic factors/profiles and overall mortality among all breast cancer women. Based on plausible biological mechanisms operating that may influence breast cancer development, we included the following covariates when studying the associations between ethnicity and breast cancer risk by pre-diagnostic metabolic factors/profiles: age, age at menarche and number of children. Additional adjustment for MHT and alcohol use did not change the estimates. We adjusted for age at diagnosis, cigarette smoking and ethnicity in the analyses of the association between pre-diagnostic metabolic factors/profiles and overall mortality.

We tested for interaction between ethnicity and metabolic profile, and between breast cancer subtype and metabolic factors. The proportional hazards assumption was assessed by visual inspection of log–log survival functions of the different ethnic groups.

We used age- and multivariable-adjusted logistic regression analyses to study the association between ethnicity and breast cancer subtype and treatment. We adjusted for age and year at diagnosis, and BMI when studying differences in breast cancer subtype by ethnicity, whereas age and year at diagnosis, BMI, and breast cancer subtype were included when studying differences in received treatment by ethnicity.

Additional adjustment for comorbidity at the time of breast cancer diagnosis, pre-diagnostic physical activity, and level of education did not change the estimates.

Statistical significance was defined as $p < 0.05$, and analysis was conducted using SPSS version 22.0.

Results

Characteristics of the study population and breast cancer cases

Among the 13,802 women included, 2,790 were in the ethnic minority group; among these women the largest group contained women from south Asia (39.3%). At study enrollment, the ethnic minority women were younger (mean age 39.2 years versus 48.6 years), and had higher BMI (mean 26.5 versus 25.1 kg/m^2) and higher TG:HDL-C (mean 1.35 versus 0.90) compared with the western European women (Table 1).

A total of 487 western European and 70 ethnic minority women were diagnosed with invasive histological verified breast cancer during a mean follow-up of 16.5 years. The ethnic minority women were younger at diagnosis compared with the western European women (mean 53.8 years versus 61.6 years), and less likely to have ER-positive tumors (73.9% versus 85.6%), more likely to present with HER2-positive tumors (22.6% versus 12.8%), histological grade 3 tumors (43.8% versus 25.6%), and to receive chemotherapy (65.2% versus 41.1%) (Table 2, Supplementary Table 1). The differences between ethnicities of those receiving chemotherapy (Table 2) were observed among women with hormone receptor-positive tumors (Supplementary Table 1).

Breast cancer risk, ethnicity and metabolic profiles

Age-adjusted overall breast cancer risk was 29% lower in ethnic minority women compared with western European women during follow-up (hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.55–0.92) (Supplementary Table 2).

We found lower breast cancer risk in the ethnic minority women compared with western European women among those with 0–2 unfavorable metabolic factors (HR 0.66, 95% CI 0.46–0.95) ($P_{interaction} = 0.056$) (Table 3). We subcategorized the ethnic minority women. Among women with four unfavorable metabolic factors, south Asian women had 2.3 times higher breast cancer risk than western European women (HR 2.30, 95% CI 1.18–4.49) ($P_{interaction} = 0.022$) (Table 3). No increased breast cancer risk was observed in the other two subcategories of ethnic minority women (Middle East/north Africa and all other non-western origins) compared with western European women among those with four unfavorable metabolic factors (data not shown).

Ethnicity and breast tumor subtype and treatment

When comparing the breast cancer cases among ethnic minority and western European women by breast cancer subtype and treatment, the ethnic minority women were more likely to present with TNBC (OR 2.11, 95% CI 0.97–4.61)

Table 1. Characteristics[a] of all participating women according to birth origin: the Oslo Ethnic Breast Cancer Study.

	Total ($n = 13,802$)[b] Mean (SD)	Western European women[a] ($n = 11,012$)[b] Mean (SD)	Ethnic minority women			
			All ethnic minority women ($n = 2790$)[b] Mean (SD)	South Asian women ($n = 1097$)[b] Mean (SD)	Middle Eastern and north African women ($n = 724$)[b] Mean (SD)	All other non-western origin women ($n = 969$)[b] Mean (SD)
Characteristics at study entry						
Age at attendance (years)	46.7 (14.8)	48.6 (15.4)	39.2 (9.92)	37.9 (9.12)	38.1 (9.25)	41.3 (10.8)
Follow-up (years)	16.5 (3.54)	16.5 (3.73)	16.7 (2.29)	16.7 (2.11)	16.7 (1.66)	16.7 (2.71)
Higher education[c] (%)	45.6	48.8	31.5	26.6	29.7	37.1
Income-generating work[d] (%)	78.4	84.7	56.5	51.8	48.6	67.7
Reproductive factors						
Number of children	1.58 (1.33)	1.41 (1.18)	2.23 (1.64)	2.40 (1.57)	2.29 (1.66)	2.00 (1.66)
Age at menarche (years)	13.4 (1.68)	13.3 (1.49)	13.7 (2.27)	13.8 (2.66)	13.3 (1.95)	13.9 (1.89)
Clinical variables						
Height (cm)	164 (7.51)	166 (6.51)	157 (6.80)	156 (5.76)	158 (7.50)	157 (7.09)
BMI (kg/m^2)	25.4 (4.55)	25.1 (4.40)	26.5 (5.01)	27.2 (4.91)	27.8 (5.43)	24.6 (4.56)
Waist:hip ratio	0.80 (0.07)	0.79 (0.07)	0.82 (0.08)	0.84 (0.08)	0.81 (0.07)	0.80 (0.07)
Systolic blood pressure (mHg)	126 (19.4)	128 (19.7)	118 (15.8)	118 (15.5)	116 (14.3)	120 (17.0)
Diastolic blood pressure (mmHg)	71.7 (11.2)	72.5 (11.2)	68.9 (10.5)	69.0 (10.3)	66.9 (9.77)	70.1 (11.2)
Serum samples						
T cholesterol (mmol/l)	5.48 (1.12)	5.60 (1.12)	5.02 (0.99)	4.94 (0.92)	4.91 (0.99)	5.17 (1.04)
HDL-C (mmol/l)	1.59 (0.42)	1.65 (0.41)	1.37 (0.35)	1.24 (0.29)	1.36 (0.32)	1.53 (0.38)
TGs (mmol/l)	1.39 (0.93)	1.31 (0.83)	1.60 (1.16)	1.84 (1.36)	1.51 (1.04)	1.41 (0.95)
TG:HDL-C	0.99 (0.98)	0.90 (0.81)	1.35 (1.41)	1.67 (1.80)	1.24 (1.09)	1.06 (0.96)
Lifestyle factors/ Comorbidity (%)						
MHT users[e]	16.8	19.8	6.75	5.58	9.30	6.20
Blood pressure treatment[f]	9.85	10.6	6.89	7.77	6.06	6.38
C-lowering treatment[g]	5.05	5.29	4.03	5.37	4.37	2.27
Diabetes mellitus	2.70	1.96	5.93	9.30	4.50	3.20
Alcohol consumption[h]	56.8	67.1	13.2	3.60	10.5	25.3
Current cigarette smokers	25.2	28.5	11.4	1.40	23.2	13.2
Moderate physical activity[i]	51.9	57.3	29.8	28.5	27.7	33.7

BMI: body mass index (kg/m^2); C: cholesterol; HDL: high-density lipoprotein; MHT: menopausal hormone therapy; *n*: number of participants; SD: standard deviation; T: total; TG: triglyceride.
[a]Western European women: women born in Norway with Norwegian ancestry and western immigrants; Nordic countries, western Europe, Australia and North America.
[b]Numbers may vary due to missing information.
[c]College and/or university education, $\geq$14 years of school.
[d]Current full- or part-time work.
[e]Previous or current MHT use.
[f]Current blood pressure treatment.
[g]Current cholesterol-lowering treatment.
[h]Alcohol consumption defined by times per month.
[i]Moderate physical activity defined by $\geq$3 h of light activity and/or $\geq$1 h heavy exercise per week.

compared with the western European women (Table 4). We observed no differences in treatment modality (type of surgery, systemic therapy and radiotherapy), but the ethnic minority women were less likely to complete all courses of taxane treatment (HR 0.26, 95% CI 0.08–0.82) compared with the western European women.

Overall mortality

Among 440 breast cancer cases with complete information on hormone receptor and HER2 status, our results indicate a relationship between pre-diagnostic unfavorable metabolic factors and overall mortality (HR 1.50, 95% CI 0.90–2.44 for 4 versus 0–2 factors, $P_{trend} = 0.078$) (Table 5, Supplementary Figure 2).

Among TNBC women, above-median TG:HDL-C (>0.73) compared with below-median TG:HDL-C (≤ 0.73) levels were associated with 2.9 times (HR 2.88, 95% CI 1.02–8.11)

($P_{interaction} = 0.004$) higher overall mortality risk (Table 5). Due to the low number of deaths among the ethnic minority breast cancer women ($n = 11$), any associations between ethnicity, metabolic factors (separately or combined) and mortality could not be studied.

Discussion

In this population-based cohort study, we observed among women with an unfavorable metabolic profile a 2.3-fold higher breast cancer risk in south Asian immigrant women compared with western European women. Thus, our findings both extend and are in part supported by others. A stronger association of BMI, weight gain and WHR with breast cancer risk was observed in postmenopausal Asian and Asian-American women than in non-Hispanic white women [24], and a dose–response association was found between unfavorable metabolic factors (high BP, diabetes and

Table 2. Breast tumor characteristics and treatment modalities for western European and ethnic minority breast cancer cases: the Oslo Ethnic Breast Cancer Study.

	Western European[a] breast cancer cases (n_{cases} = 487)[b] Mean (SD)	Ethnic minority breast cancer cases (n_{cases} = 70)[b] Mean (SD)
Age at diagnosis (years)	61.6 (12.7)	53.8 (8.43)
Follow- up after diagnosis (years)	7.85 (5.31)	7.11 (6.10)
Tumor characteristics		
Histological subtype (%)		
Invasive carcinoma NST	78.3	92.2
Invasive lobular carcinoma	12.7	3.10
Others	9.00	4.70
Tumor size (mm)	22.4 (19.0)	24.3 (20.1)
Lymph node positive (%)	35.1	29.9
Disease stage (%)		
1–2	84.5	80.6
3	12.6	17.9
4	2.90	1.50
Histological grading (%)		
1	25.6	21.9
2	48.8	34.4
3	25.6	43.8
ER positive (%)	85.6	73.9
PgR positive (%)	65.8	58.5
HER2 positive (%)	12.8	22.6
Ki-67 %	29.8 (21.6)	33.0 (19.2)
Treatment (%)		
Mastectomy	35.7	37.9
Breast-conserving treatment	57.0	59.1
Other type of surgery	3.50	3.00
SN dissection	64.7	65.1
Axillary dissection	32.1	34.9
Treatment intention		
Curative	94.9	98.5
Palliative	5.10	1.50
Chemotherapy	41.1	65.2
Anthracyclines[c]	38.8	63.6
Taxanes[d]	20.0	36.4
Endocrine therapy	57.9	55.4
Tamoxifen	30.7	30.7
Aromatase inhibitors	35.4	24.6
Trastuzumab	9.35	14.7
Radiotherapy	73.0	87.5
Local radiation	64.2	60.7
Locoregional radiation	35.8	39.3

[a]Western European women: women born in Norway with Norwegian ancestry and western immigrants; Nordic countries, western Europe, Australia and North America.
[b]Numbers may vary due to missing information.
[c]FEC-60, FEC-100 or EC-90.
[d]Paclitaxel or docetaxel.
EC: epirubicin; cyclophosphamide; ER: estrogen receptor; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; HER2; human epidermal growth factor receptor-2; NST: no special type; PgR: progesterone receptor; SN: sentinel node.

dyslipidemia) and breast cancer risk among Asian-Americans born or residing in the USA for >20 years [25]. Ethnic disparities in BMI and risk for other chronic diseases have been observed [26], and, based on the same population as in the present study, a high prevalence of obesity-dependent type 2 diabetes was found among women from Pakistan and Sri Lanka [6]. Moreover, a BMI-independent association between type 2 diabetes and breast cancer risk may vary with ethnicity [27].

A stronger adverse effect of an unfavorable metabolic profile on breast cancer risk in women of Asian ancestry may be explained in part by the higher proportion of visceral than subcutaneous adipose tissue among Asian compared with non-Hispanic white women [28], and visceral adiposity is more strongly associated with an adverse metabolic profile [28]. Consequently, ethnic specific criteria of being

overweight (BMI) and abdominal obesity (waist circumference) defines women from south Asia as overweight at a lower BMI and a lower waist circumference compared with the overweight definitions for Europeans [29]. Interestingly, white adipose tissue (WAT) inflammation in the breast, a proposed link between chronic subclinical inflammation and breast cancer development, is highly correlated with BMI, insulin resistance and TGs [30]. WAT inflammation was observed to be higher in Asian breast cancer women compared with US non-Hispanic white women, despite lower BMIs, suggesting that a subclinical inflammatory state may contribute to breast cancer pathogenesis in these women [30].

Our results showing a lower age-adjusted breast cancer risk in ethnic minority women compared with the western European women is supported [31]. However, in contrast to

Table 3. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for breast cancer risk comparing all ($n = 2,790$) ethnic minority women with western European women ($n = 11,012$), and south Asian women ($n = 1097$) with western European women, by metabolic factors and metabolic profiles: the Oslo Ethnic Breast Cancer Study.

	n_{cases}	Western European women[a] ($n = 11,012$) HR (95% CI)	n_{cases}	Ethnic minority women[b] ($n = 2,790$) HR (95% CI)
Metabolic factors				
BMI				
≤24.6 kg/m^2	245	1.00 (ref)	18	0.34 (0.27–0.74)
>24.6 kg/m^2	242	1.00 (ref)	52	1.16 (0.82–1.62)
WHR				
≤0.79	273	1.00 (ref)	29	0.75 (0.50–1.10)
>0.79	214	1.00 (ref)	41	0.88 (0.61–1.29)
TG:HDL-C				
≤0.73	268	1.00 (ref)	22	0.67 (0.43–1.06)
>0.73	219	1.00 (ref)	48	0.90 (0.64–1.29)
BP[c]				
≤96.5 mmHg	212	1.00 (ref)	38	0.66 (0.46–0.95)
>96.5 mmHg	275	1.00 (ref)	32	1.03 (0.70–1.53)
Metabolic profile[d]				
Cat. 1:0–2 factors	311	1.00 (ref)	35	0.66 (0.46–0.95)
Cat. 2: 3 factors	93	1.00 (ref)	17	0.88 (0.48–1.62)
Cat. 3: 4 factors	83	1.00 (ref)	18	1.53 (0.86–2.71)
	n_{cases}	Western European women[a] ($n = 11,012$) HR (95% CI)	n_{cases}	South Asian women ($n = 1,097$) HR (95% CI)
Metabolic factors				
BMI				
≤24.6 kg/m^2	245	1.00 (ref)	6	0.51 (0.22–1.17)
>24.6 kg/m^2	242	1.00 (ref)	25	1.29 (0.82–2.03)
WHR				
≤0.79	273	1.00 (ref)	6	0.63 (0.28–1.44)
>0.79	214	1.00 (ref)	25	1.13 (0.71–1.79)
TG:HDL-C				
≤0.73	268	1.00 (ref)	3	0.38 (0.12–1.19)
>0.73	219	1.00 (ref)	28	1.16 (0.75–1.80)
BP[c]				
≤96.5 mmHg	212	1.00 (ref)	13	0.62 (0.35–1.14)
>96.5 mmHg	275	1.00 (ref)	18	1.47 (0.90–2.46)
Metabolic profile[d]				
Cat. 1: 0–2 factors	311	1.00 (ref)	9	0.60 (0.30–1.18)
Cat. 2: 3 factors	93	1.00 (ref)	9	0.93 (0.43–2.00)
Cat. 3: 4 factors	83	1.00 (ref)	13	2.30 (1.18–4.49)

Cox's proportional hazard regression.
[a]Western European women: women born in Norway with Norwegian ancestry and western immigrants; Nordic countries, western Europe, Australia and North America.
[b]South Asia, Middle East and north Africa, eastern Europe, East Asia, sub-Saharan Africa, South and Central America.
[c]BP = (SBP + DBP)/2.
[d]Factors included: Above median levels of BMI (>24.6 kg/m^2), WHR (>0.79), TG:HDL-C (>0.73) and BP (>96.5 mmHg). Adjusted for age, age at menarche, number of children.
BMI: body mass index; BP: blood pressure; Cat.: category; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein-cholesterol; n: number of participants; n_{cases}: number of cases; ref: reference; SBP: systolic blood pressure; TG: triglycerides; WHR: waist:hip ratio.

a recent register study [9], we observed no overall differences in breast cancer risk between women of south Asian background and the western European women. This discrepancy may be explained by a lower sample size in our study. Of importance, inclusion of breast cancer cases in our study was from a later time period after immigration compared with the register study (2000–18 versus 1990–2012), resulting in a potentially higher cumulative dose of unfavorable lifestyle changes. Our results are supported by observations suggesting a time-dependent attenuation of the protective effect of ethnicity on breast cancer risk among non-western immigrants moving from a low- to a high-incidence country [2,32].

We observed an increased likelihood of TNBC in ethnic minority compared with western European breast cancer women, also observed by others [11]. Higher incidence of

obesity, insulin resistance and premenopausal TNBC was observed in African-American women, supporting a mechanistic link of an unfavorable metabolic profile, ethnicity and this aggressive breast cancer subtype [33]. Our results concerning disease-stage presentation at diagnosis differ from previous studies in Norway [12] and others [11,34,35], which have shown that immigrant women have higher risk of presenting a more advanced disease stage at diagnosis than the western majority women.

In the present study no differences by ethnicity were observed in physicians' decisions of planned breast cancer treatment by breast cancer subtype, in line with other studies based on data from comparable populations and healthcare systems [36]. However, ethnic minority breast cancer women were less likely to complete their taxane courses. Poor adherence and completion of breast cancer adjuvant/

Table 4. Age- and multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) comparing ethnic minority women and western European women by breast cancer subtype and received treatment.

	Western European breast cancer cases[a] (n_{cases} = 381)		Ethnic minority breast cancer cases (n_{cases} = 59)		
	n_{cases}	OR (95% CI)	n_{cases}	Age-adjusted OR (95% CI)	Multivariable-adjusted[b] OR (95% CI)
Breast cancer subtype[c]					
Hormone receptor-positive BC	294	1.00 (ref)	35	0.69 (0.41–1.15)	0.47 (0.26–0.86)
HER2-positive BC	49	1.00 (ref)	13	1.51 (0.76–3.00)	1.68 (0.81–3.50)
Triple-negative BC	38	1.00 (ref)	11	2.27 (1.07–4.79)	2.11 (0.97–4.61)
Breast cancer treatment[d]					
Curative treatment intention	361	1.00 (ref)	58	1.29 (0.16–10.6)	1.36 (0.16–11.3)
Mastectomy	136	1.00 (ref)	20	1.12 (0.61–2.02)	0.94 (0.51–1.75)
Breast conservative treatment	213	1.00 (ref)	36	1.01 (0.56–1.82)	1.20 (0.65–2.21)
SN dissection	242	1.00 (ref)	41	1.24 (0.67–2.29)	1.37 (0.73–2.56)
Axillary lymph node dissection	125	1.00 (ref)	17	0.73 (0.39–1.35)	0.64 (0.34–1.21)
Endocrine therapy	228	1.00 (ref)	31	0.79 (0.45–1.41)	1.05 (0.55–2.04)
Tamoxifen	109	1.00 (ref)	16	0.68 (0.36–1.28)	0.77 (0.39–1.52)
Aromatase inhibitor	153	1.00 (ref)	14	0.62 (0.32–1.20)	0.73 (0.37–1.44)
Chemotherapy	179	1.00 (ref)	38	1.22 (0.65–2.29)	0.85 (0.42–1.71)
Anthracyclines	171	1.00 (ref)	37	1.27 (0.68–2.23)	0.94 (0.48–1.83)
Complete anthracyline courses[e]	131	1.00 (ref)	29	1.02 (0.43–2.43)	1.02 (0.41–2.52)
Taxanes	90	1.00 (ref)	24	1.65 (0.91–2.99)	1.32 (0.69–2.54)
Complete taxane courses[f]	63	1.00 (ref)	15	0.25 (0.08–0.76)	0.26 (0.08–0.82)
Trastuzumab	42	1.00 (ref)	10	1.18 (0.55–2.56)	0.85 (0.37–1.96)
Radiotherapy	280	1.00 (ref)	49	1.28 (0.54–3.04)	1.37 (0.57–3.28)
Local radiotherapy	168	1.00 (ref)	32	1.42 (0.74–2.72)	1.60 (0.82–3.13)
Locoregional radiotherapy	110	1.00 (ref)	17	0.70 (0.37–1.35)	0.62 (0.32–1.22)

Logistic regression analysis.
[a]Western European women: women born in Norway with Norwegian ancestry and western immigrants; Nordic countries, western Europe, Australia and North America.
[b]Breast cancer subtype is adjusted for age at diagnosis, year of diagnosis and body mass index (kg/m^2). Breast cancer treatment is adjusted for age at diagnosis, year of diagnosis, body mass index (kg/m^2) and breast cancer subtype.
[c]Hormone receptor-positive BC: ER positive (with or without PgR positive) and HER2 negative; HER2-positive BC: all patients with HER2 overexpression; triple-negative BC: ER-, PgR- and HER2 negative.
[d]Adjuvant breast cancer treatment.
[e]Six courses of FEC-60, four to six courses of FEC-100, or four courses of EC-90.
[f]Either 12 courses of weekly paclitaxel or 4 courses of docetaxel.
BC: breast cancer; EC: epirubicin, cyclophosphamide; ER: estrogen receptor; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; HER2: human epidermal growth factor receptor-2; n_{cases}: number of cases; PgR: Progesterone; ref: reference; SN: sentinel node.

Table 5. Multivariable-adjusted hazard ratios (HRs) for overall mortality by metabolic risk factors (median split) and metabolic profiles (categories) among all breast cancer cases and according to breast cancer subtype: the Oslo Ethnic Breast Cancer Study.

	n_{cases}	All breast cancer cases (deaths = 95) HR (95% CI)	n_{cases}	Hormone receptor-positive breast cancer[a] (deaths = 69) HR (95% CI)	n_{cases}	HER2 positive-breast cancer[b] (deaths = 9) HR (95% CI)	n_{cases}	Triple-negative breast cancer[c] (deaths = 17) HR (95% CI)
Metabolic factors[d]								
BMI								
≤24.6 kg/m^2	215	1.00 (ref)	153	1.00 (ref)	38	1.00 (ref)	24	1.00 (ref)
>24.6 kg/m^2	225	1.15 (0.75–1.76)	175	1.11 (0.68–1.83)	24	3.39 (0.82–14.0)	26	0.84 (0.31–2.25)
WHR								
≤0.79	252	1.00 (ref)	182	1.00 (ref)	47	1.00 (ref)	23	1.00 (ref)
>0.79	188	1.46 (0.90–2.36)	147	1.85 (1.05–2.15)	15	0.56 (0.11–2.95)	26	1.10 (0.34–3.52)
TG:HDL-C								
≤0.73	232	1.00	169	1.00 (ref)	37	1.00 (ref)	26	1.00 (ref)
>0.73	208	1.53 (0.98–2.40)	160	1.20 (0.70–2.07)	25	1.71 (0.38–7.70)	23	2.88 (1.02–8.11)
BP[e]								
≤96.5 mmHg	208	1.00 (ref)	150	1.00 (ref)	39	1.00 (ref)	19	1.00 (ref)
>96.5 mmHg	232	1.35 (0.83–2.22)	179	1.01 (0.57–1.78)	23	1.07 (0.24–4.71)	30	4.77 (1.01–22.6)
Metabolic profiles[f]								
Cat. 1 :0–2 factors	284	1.00	207	1.00 (ref)	50	1.00 (ref)	27	1.00 (ref)
Cat. 2: 3 factors	76	1.53 (0.91–2.55)	58	1.72 (0.95–3.15)	7	1.56 (0.16–15.0)	11	0.83 (0.25–3.82)
Cat. 3: 4 factors	80	1.50 (0.92–2.44)	64	1.53 (0.87–2.70)	5	0.95 (0.10–9.34)	11	1.80 (0.53–6.11)
P trend		0.078		0.112		0.935		0.449

Cox's proportional hazard model.
[a]Hormone receptor-positive BC: ER positive (with or without PgR positive).
[b]HER2-positive BC: all patients with HER2 overexpression.
[c]Triple-negative BC: ER-, PgR- and HER2 negative.
[d]Adjusted for age at diagnosis, BMI (excluding median splits of BMI), smoking habits, and ethnicity.
[e]BP = (SBP + DBP)/2.
[f]Factors included: above median levels of BMI (>24.6 kg/m^2), WHR (>0.79), TG:HDL-C (>0.73) and BP (>96.5 mmHg). Adjusted to age at diagnosis, smoking habits, and ethnicity.
BMI: body mass index; BP: blood pressure; Cat: category; DBP: diastolic blood pressure; ER: estrogen receptor; HER2: human epidermal growth factor receptor-2; HDL: high-density lipoprotein-cholesterol; n: number of cases; PgR: progesterone receptor; ref: reference; SBP: systolic blood pressure; TG: triglycerides; WHR: waist:hip ratio.

neoadjuvant chemotherapy have been associated with adiposity, physical inactivity, poor social support and black race, rather than being non-Hispanic white [37]. Adjusting for BMI and physical activity did not change our estimates, and incompletion of taxanes was primarily present among ethnic minority women with TNBC.

An associations between an unfavorable lifestyle/metabolic factors and overall mortality [23,38] and breast cancer mortality [39,40] have been observed, and between TG levels and overall mortality and breast cancer recurrence among TNBC patients [41]. Moreover, insulin resistance, TG levels and WAT inflammation have been associated with tumor aggressiveness and progression among TNBC patients [42,43]. Thus, key mechanisms linking pre-diagnostic TGs and TG:HDL-C to TNBC prognosis are supported, but need to be further elucidated.

Our study has several strengths, which include its population-based approach, the use of a standardized protocol for data collection, measured height, weight and BP, and trained personnel who checked the questionnaires for inconsistencies. Detailed medical records for the breast cancer patients were carefully reviewed by trained physicians, and the definition of ethnicity used in our study has been observed to be valid [44]. A high completeness rate (98.8%) of identification of breast cancer cases (Cancer Registry of Norway) has been observed and validated [20], and the identification of death and emigration are included (Cause of Death Registry). These strengths limit the possibility for any misclassification related to identification of cases, and it is less likely that loss to follow-up or inadequate reporting influences our risk estimate.

The present study also has limitations. The attendance rate in the Oslo Health Studies was only about 50%, which could introduce selection bias [14], but there were minor variations in attendance rates between the different ethnic groups, and subjects with low socioeconomic status were under-represented in all groups. Thus, the prevalence of unfavorable metabolic factors is more likely to be under-estimated than over-estimated [45]. Blood samples were not collected in a fasting state, but adjustment for time since last meal did not change our estimates. Previous studies suggest that the lower breast cancer incidence in south Asian immigrants may be due to reduced utilization of Norwegian healthcare services, including mammographic screening [46], and one may propose that these women are also more prone to nonattendance in public screening programs [14]. Consequently, our cohort may include the more socially and culturally westernized ethnic minority women. The low number of breast cancer cases among the ethnic minority women limited the possibility of performing stratified analyses by i.e., menopausal status and breast cancer subtype, and survival analyses by ethnicity.

In conclusion, our results support the importance of metabolic factors when balancing breast cancer prevention and disease management among non-western women migrating from a breast cancer low-incidence to a high-incidence country. Our observation prompts more and larger studies, including immigrant women in western countries, to improve and tailor personal lifestyle advice to prevent breast cancer development and optimize breast cancer treatment.

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Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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