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ABO blood group and breast cancer incidence and survival

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Abstract

ABO blood type has been associated with risk and survival for several malignancies; however, data for an association with breast cancer are inconsistent. Our study population consisted of Nurses' Health Study participants with self-reported serologic blood type and/or *ABO* genotype. Using Cox proportional hazards regression, we examined the association between serologic blood type and incident breast cancer among 67,697 women, including 3,107 cases. In addition, we examined the association with *ABO* genotype in a nested case-control study of 1,138 invasive breast cancer cases and 1,090 matched controls. Finally, we evaluated the association between serologic blood type and survival among 2,036 participants with breast cancer. No clear association was seen between serologic blood type or *ABO* genotype and risk of total breast cancer, invasive breast cancer, or breast cancer subtypes. Compared to women with blood type O, the age-adjusted incidence rate ratios for serologic blood type and total breast cancer were 1.06 (95% CI, 0.98–1.15) for type A, 1.06 (95% CI, 0.93–1.22) for AB, and 1.08 (95% CI, 0.96–1.20) for B. In genetic analyses, odds ratios for invasive breast cancer were 1.05 (95% CI, 0.87–1.27) for *A/O*, 1.21 (95% CI, 0.86–1.69) for *A/A*, 0.84 (95% CI, 0.56–1.26) for *A/B*, 0.84 (95% CI, 0.63–1.13) for *B/O*, and 1.17 (95% CI, 0.35–3.86) for *B/B*, compared to *O/O*. No significant association was noted between blood type and overall or breast cancer-specific mortality. Our results suggest no association between ABO blood group and breast cancer risk or survival.

Keywords

ABO blood group; *ABO* genotype; blood type; breast cancer; survival

INTRODUCTION

ABO blood type has been associated with risk and survival for several malignancies;[1–8] however, the evidence for an association with breast cancer is inconsistent.[9–15] Older studies of blood type and breast cancer risk generally reported no association.[9–11] However, a recent study was suggestive of a possible association between blood group A and increased risk of ductal carcinoma,[13] and two studies reported an association between blood group A[14] or B[15]

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and increased risk of familial breast cancer. These studies suggest the possibility that associations may exist between ABO blood type and specific breast cancer subtypes that were not detected in previous studies of all breast cancers combined. Associations with Rh factor have also been inconsistent,[9, 12, 16–18] as have studies of ABO blood type and breast cancer survival.[19–21]

The *ABO* gene on chromosome 9q34 encodes glycosyltransferases that catalyze the transfer of nucleotide donor sugars to the H antigen to form the ABO blood group antigens.[22] In addition to their expression on red blood cells, the A and B isoantigens are expressed on the surface of normal breast ductal cells and are weakly expressed on normal breast lobular cells.[23, 24] Some malignant breast tumors lose ABO antigen expression, while benign lesions vary with respect to antigen expression,[23–25] suggesting a possible role of ABO blood group antigens in breast carcinogenesis. Some studies also suggest a possible association between blood group antigen expression and prognostic factors among breast cancer patients.[26, 27]

We conducted a comprehensive, prospective analysis of ABO blood group and breast cancer incidence and survival in the Nurses' Health Study (NHS). We examined the association with self-reported serologic blood type among 67,697 women, including 3,107 incident cases of breast cancer. In addition, we examined the association between *ABO* genotype and breast cancer risk using genetic data from a previously completed genome-wide association study. Finally, we evaluated the association between self-reported serologic blood type and survival in women with invasive breast cancer.

MATERIALS AND METHODS

Study population

The NHS began in 1976 when 121,700 U.S. female registered nurses ages 30 to 55 years completed a mailed questionnaire about known and suspected risk factors for cancer and cardiovascular disease. Participants have completed follow-up questionnaires every two years, providing updated information on lifestyle factors and disease diagnoses. Additional details of the study design are available elsewhere.[28] The Committee on the Use of Human Subjects in Research at Brigham and Women's Hospital, Boston, MA approved this study and all participants provided implied consent by completing the baseline questionnaire.

Exposure assessment

Participants reported their blood type (A, AB, B, O, unknown) and Rh factor (positive, negative, unknown) on the 1996 questionnaire. Seventy-seven percent of respondents provided their blood type, and 95% of these women also provided their Rh type. Among women who answered this questionnaire, follow-up rates were 97.9% of the total possible person-years through June 2006.

In 1989 and 1990, 32,826 NHS participants provided a blood sample for use in genetic and other biomarker analyses. Details of the blood collection are described elsewhere.[29] Briefly, participants arranged to have their blood drawn and shipped with an icepack via overnight mail. Upon receipt at our laboratory, each blood specimen was processed and stored in continuously-monitored liquid nitrogen freezers at a temperature of −130°C or colder.

We determined *ABO* genotype for incident, invasive, postmenopausal breast cancer cases and matched controls using single nucleotide polymorphism (SNP) data from the Cancer Genetic Markers of Susceptibility (CGEMS) project. Cases and controls were matched on year of birth, menopausal status, and postmenopausal hormone (PMH) use at blood draw, and all participants were of self-reported European ancestry. Samples were genotyped with the Illumina HumanHap500 array; additional details are provided elsewhere.[30] We used the

rs505922, rs8176704, and rs8176746 SNPs to infer each participant's phased haplotypes with >99% posterior probability, based on an expectation-maximization algorithm.[31] The rs8176746 polymorphism is a marker of the *B* allele, while rs505922 is perfectly correlated with rs687289, a marker of the *O* allele.[4, 32] We additionally used rs8176704 to distinguish between the two most common *A* alleles, A^1 and A^2.[32] The A^1 allele is associated with 30–50 fold higher activity of the A glycosyltransferase than the A^2 allele.[32] Using the inferred haplotype data, we determined each individual's genotype (*O/O*, *A/O*, *A/A*, *A/B*, *B/O*, or *B/B*) and the number of A^1, A^2, and *B* alleles (0, 1, or 2).

Covariates

We collected data on covariates of interest on one or more questionnaires during follow-up. Height, age at menarche, and age at first birth were reported in 1976, and weight at age 18 was reported in 1980. Participants reported their major ancestry in 1992, and race and ethnicity were assessed in 2004. Questions on parity, menopausal status, PMH use, current weight, smoking status, alcohol intake, history of benign breast disease (BBD), and family history of breast cancer were included on multiple questionnaires during follow-up. In our analysis, we updated the values for these covariates when new data were available and otherwise carried forward the values from the previous cycle or the last cycle where each covariate was assessed.

Identification of breast cancer cases and deaths

We collected information on new diagnoses of breast cancer on each biennial questionnaire. For all reported cases, as well as deaths due to breast cancer, we requested medical records related to the diagnosis. We confirmed cases using pathology reports or cancer registry data whenever possible, and otherwise by obtaining written or verbal confirmation from the study participant or death certificate information. Over 93% of the invasive breast cancer cases were confirmed by medical record review. Information on histologic type, estrogen and progesterone receptor (ER/PR) status, and other tumor characteristics was extracted from the medical records.

Deaths were identified through family members, the National Death Index, or the U.S. Postal Service. Over 98% of deaths in the Nurses' Health Study are captured by these methods.[33, 34] Physicians blinded to exposure status reviewed the medical records and/or death certificates to ascertain the cause of death.

Statistical analysis

Of 100,955 women who answered the 1996 questionnaire, we excluded 23,545 who did not report their blood type and 9,713 who were diagnosed with cancer other than nonmelanoma skin cancer prior to 1996. Participants accrued person-time from the return date of the 1996 questionnaire until the date of breast cancer diagnosis, diagnosis of any other cancer (excluding nonmelanoma skin cancer), death, or the end of follow-up, June 1, 2006.

In a prospective cohort analysis of self-reported serologic blood type and breast cancer incidence, we used Cox proportional hazards regression to model the incidence rate ratios (RR) and 95% confidence intervals (CI) of breast cancer for each category of ABO blood type, compared to type O. We evaluated associations with several breast cancer subtypes, including ductal and lobular cancers, HER2/neu positive cancers, and case groups defined by ER/PR status. In addition, we examined the association with Rh factor (Rh negative versus positive) and presence versus absence of the A or B antigen (e.g., blood type AB/B versus O/A).

We evaluated several covariates as potential confounders, including parity, age at first birth, duration of oral contraceptive use, duration of breastfeeding, age at menarche, menopausal status, history of BBD, family history of breast cancer, body mass index (BMI), alcohol use, duration of PMH use, and race/ethnicity. All estimates were unchanged after controlling for these variables; we therefore adjusted our final incidence models for continuous age in months only.

We assessed whether the association between serologic blood type and breast cancer incidence differed by level of several potential effect modifiers, including age, menopausal status, PMH use, BMI, smoking history, family history of breast cancer, and Rh factor. We tested for effect modification by modeling product interaction terms between each potential modifier of interest and indicator variables for each blood type category, and calculating likelihood ratio tests.

In a nested case-control analysis of 1,138 invasive breast cancer cases and 1,090 matched controls, we used unconditional logistic regression to model the age-adjusted odds ratios (OR) and 95% CIs for the association between *ABO* genotype and risk of invasive cancers, ductal cancers, and hormone receptor positive (ER and/or PR positive) cancers. We also estimated per-allele ORs by including continuous variables for the number of A^1, A^2, and B alleles in a single model, to control the estimates for the presence of other alleles. Of the 1,138 breast cancer cases included in the nested case-control analysis, 579 (51%) were also included in the prospective analysis described above.

Finally, in an analysis of self-reported blood type and survival among invasive breast cancer cases, we used Cox proportional hazards regression to model multivariable-adjusted hazard ratios (HR) and 95% CIs for total and breast cancer-specific mortality. Of 2,512 invasive cases diagnosed between 1996 and 2006, 476 were excluded because they were metastatic at diagnosis or had missing stage information; of the 2,036 invasive cases included in the analysis, 107 died due to breast cancer and 152 died due to other causes. We used time since diagnosis in months as the underlying time variable, to carefully control for confounding by time of diagnosis. Cases accrued person-time from the date of diagnosis until the date of death or June 1, 2008, whichever occurred first. We adjusted all analyses for age at diagnosis, date of diagnosis, disease stage, radiation treatment, chemotherapy and/or hormonal therapy, and ER/PR status. In addition, we adjusted the analyses for physical activity after diagnosis/treatment and the following exposures at the time of diagnosis: smoking status, BMI, menopausal status/PMH use, parity/age at first birth, oral contraceptive use, and family history of breast cancer.

RESULTS

Analyses of incident breast cancers

The prospective cohort analysis included 67,697 women with 617,233 person-years of follow-up, and 595 *in situ* and 2,512 invasive cases of incident breast cancer. Of the invasive cases, 1,877 were ductal (75%), 300 were lobular (12%), 121 were both ductal and lobular (5%), 31 had no primary structure evident (1%), and 183 were unknown/missing (7%). A total of 2,175 invasive cases (87%) had data on ER/PR status and 1,457 (58%) had data on HER2/neu status; 1,466 cases were ER+/PR+ (67%), 339 were ER+/PR− (16%), 37 were ER−/PR+ (2%), and 333 were ER−/PR− (15%), while 280 cases were HER2/neu positive (19%) and 1,177 were HER2/neu negative (81%).

There were no differences in the baseline characteristics of study participants by blood type, indicating that ABO blood group is unrelated to known risk factors for breast cancer (Table 1). Forty-three percent of the women in our study population reported blood type O, 36%

type A, 8% type AB, and 13% type B. This frequency distribution is similar to that reported previously for white, non-Hispanic individuals in the U.S.[35] The concordance between self-reported blood type and genotyped blood group in our population was 88.5%.

We did not observe significant associations between self-reported blood type and incidence of all (invasive plus *in situ*) cancers, invasive cancers, or any breast cancer subtype in the prospective cohort analysis (Table 2). Compared to women with blood type O, the RRs for the association with total breast cancer were 1.06 (95% CI, 0.98–1.15) for blood type A, 1.06 (95% CI, 0.93–1.22) for AB, and 1.08 (95% CI, 0.96–1.20) for B. The results were similar for invasive cancers, ductal cancers, and ER+/PR+ cancers, and there was no clear evidence of an association for the less common subtypes. In addition, there was no significant association for Rh factor (RR=0.92, 95% CI=0.84–1.00 for Rh negative versus Rh positive) or presence versus absence of the A or B antigen and incidence of all breast cancers (data not shown). The results were similar when we restricted our analyses to women who were postmenopausal in 1996 or women of self-reported European ancestry (data not shown).

Similarly, in the nested case-control analysis there was no clear association for *ABO* genotype and incidence of invasive, ductal, or hormone receptor positive (ER+ and/or PR+) cancers (Table 3). Compared to women with two *O* alleles, the ORs for invasive cancer were 1.05 (95% CI, 0.87–1.27) for genotype *A/O*, 1.21 (95% CI, 0.86–1.69) for *A/A*, 0.84 (95% CI, 0.56–1.26) for *A/B*, 0.84 (95% CI, 0.63–1.13) for *B/O*, and 1.17 (95% CI, 0.35–3.86) for *B/B*. The per-allele OR for the association with invasive cancer was 1.11 (95% CI, 0.95–1.28) for A^1, 0.97 (95% CI, 0.76–1.23) for A^2, and 0.85 (95% CI, 0.68–1.07) for *B*. We were unable to examine the associations between *ABO* genotype and the rarer breast cancer subtypes, due to the small number of cases with the less common genotypes.

We observed a nominally statistically significant interaction between self-reported blood type and total pack-years of smoking (*P*-interaction=0.03), but there was no evidence of an interaction with any other covariate examined (Table 4). In stratified analyses, positive associations with the non-O blood types were present among women with ≥25 pack-years of smoking but not among never smokers or women with <25 pack-years of smoking, although the estimates were statistically significant for blood types A and B only. The results were similar when we stratified by never, past, or current smoking in 1996, but the *P*-value for interaction was not statistically significant (*P*-interaction=0.15). There was no evidence of an interaction between Rh factor and any variable examined (data not shown).

Survival analysis

Characteristics of the 2,036 invasive cases in the survival analysis, including disease stage, ER/PR status, and treatment history, were similar across categories of self-reported blood type (Table 5). There was no significant association between blood type and total mortality or breast cancer-specific mortality. Compared to cases with blood type O, the HRs of death due to any cause were 1.00 (95% CI=0.74–1.34) for blood type A, 1.35 (95% CI=0.87–2.08) for AB, and 0.81 (95% CI=0.52–1.25) for B. The results were similar when we restricted the analysis to women who were postmenopausal in 1996. In addition, there was no evidence of an association with Rh factor or presence of the A or B antigen (data not shown).

DISCUSSION

Our results do not provide support for an association between ABO blood group and breast cancer risk or survival. We did not observe significant associations between serologic ABO blood type and incidence of total breast cancer or any breast cancer subtype, or between *ABO* genotype and risk of invasive, ductal, or hormone receptor positive cancers. The

results did not vary across a range of possible or confirmed breast cancer risk factors, with the possible exception of smoking history. No significant associations were noted between serologic blood type and overall or breast cancer-specific mortality.

Although some previous studies have reported significant associations between ABO blood group or Rh factor and breast cancer risk, overall the literature is inconsistent. The majority of the larger studies published to date observed no association with Rh factor[9, 17, 18] and/or ABO blood group,[9–11, 17, 18, 36] while smaller studies tended to report significant associations.[12, 13, 16, 37, 38] Three studies of ABO blood type reported positive associations between type A and risk of breast carcinoma[21, 38] or the ductal subtype[13] while a fourth study reported a positive association between type O and breast cancer risk.[37] In addition, two studies observed positive associations with type A or B among women with a family history of breast cancer.[14, 15] Among studies of Rh factor, two studies observed an increased risk of breast cancer among Rh negative women,[12, 16] and in the larger study the association was strongest among women with a family history of breast cancer.[12] The associations with breast cancer survival also have been mixed, with two studies reporting poorer survival among cases with blood group AB or B[19] or any non-O blood group,[20] and a third study reporting no association.[21] Several of the previous studies were limited by the small number of cases included in the analysis. Other possible reasons for the heterogeneity across studies include the use of retrospective cases, hospital-based controls, or other differences in population characteristics.

Although ABO blood group has been linked with risk for several tumor types, including gastric[1, 2, 8] and pancreatic cancer,[1, 3–5, 39, 40] the biologic mechanisms underlying these associations remain uncertain. The *ABO* gene encodes a glycosyltransferase with three main variant alleles (A, B, and O) with different substrate specificities.[41] The A, B, and O glycosyltransferases transfer N-acetylgalactosamine, D-galactose, or no sugar residue, respectively, to a protein backbone known as the H antigen.[22] Blood group antigens are expressed on the surface of red blood cells and numerous other tissues throughout the body, including breast ductal and lobular cells.[22–24] Alterations in ABO antigen expression on the surface of malignant cells, compared to normal epithelium, have been seen for a variety of tumor types, including breast cancer.[23, 24, 42] Modified expression of blood group antigens on the surface of cancer cells may alter cell motility, sensitivity to apoptosis, and immune escape, with important implications for malignant progression.[43] In addition, recent studies have reported associations between *ABO* genotype and circulating levels of tumor necrosis factor-alpha[44] and soluble ICAM-1,[32, 45] E-selectin,[46, 47] and P-selectin,[45] suggesting that blood group antigens may influence the systemic inflammatory response. Chronic inflammation has been extensively linked with malignant initiation and spread,[48] and provides a further potential mechanism by which ABO antigens may influence cancer risk.

To our knowledge, this is the first prospective analysis of ABO blood group and breast cancer risk and the largest study conducted to date. In addition to the large total number of cases, we had sufficient power to examine associations with several breast cancer subtypes and interactions with potential effect modifiers. Additional strengths of our analysis include the high follow-up rate, the availability of detailed covariate data collected prospectively and updated every two years, and physician review of medical records to establish breast cancer diagnoses and determine tumor characteristics. Although the use of self-reported blood type introduced some exposure misclassification, the results were essentially unchanged when we examined the association with imputed *ABO* genotype for a subset of our study population. In addition, our validation studies have demonstrated approximately 90% concordance between blood type determined by self-report and medical record review[3] or genotyping.[4] Our study population was composed of health care professionals and the vast majority were of self-reported European ancestry, which somewhat limits the generalizability of our

results. However, the distribution of blood types among participants in our study was similar to that of the general U.S. population,[3] and the associations would not be expected to differ by race or ethnicity.

In summary, our results suggest no association between ABO blood group and breast cancer incidence or survival.

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Abbreviations

BBD	Benign breast disease
BMI	Body mass index
CI	Confidence interval
ER	Estrogen receptor
HR	Hazard ratio
NHS	Nurses' Health Study
OR	Odds ratio
PMH	Postmenopausal hormone
PR	Progesterone receptor
RR	Incidence rate ratio
SNP	Single nucleotide polymorphism

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Novelty and impact of paper

Recent studies suggest a possible role of ABO blood group in carcinogenesis; however, prior breast cancer analyses have been inconsistent. The results of this large, comprehensive analysis of women in the Nurses' Health Study suggest no association between ABO blood group and breast cancer risk or survival.

Table 1

Baseline characteristics in 1996 by self-reported ABO blood type among 67,697 women in the Nurses' Health Study*

Characteristic	ABO blood type			
	O	A	AB	B
Number of women	29,108	24,099	5,346	9,144
% of total	43.0	35.6	7.9	13.5
Mean age in years	62	62	63	62
Mean age at menarche	13	13	13	13
Mean age at first birth among parous women	25	25	25	25
Mean parity among parous women	3.2	3.2	3.2	3.2
Mean body mass index, kg/m^2	26.7	26.6	26.5	26.7
Mean alcohol consumption, g/day	5.0	4.9	5.2	4.8
Rh factor present, %	77	79	77	78
European ancestry, %	97	98	97	96
Postmenopausal, %	88	88	89	88
Current use of postmenopausal hormones, %	45	46	44	44
Past or current smoker, %	56	55	57	56
History of benign breast disease, %	20	21	19	19
Family history of breast cancer, %	14	14	14	13

*Standardized by age in six categories (<55, 55–59, 60–64, 65–69, 70–75, ≥75)

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Table 2

Incidence rate ratios (RR) and 95% confidence intervals (CI) for the association between self-reported ABO blood type and incidence of breast cancer among 67,697 women in the Nurses' Health Study

	ABO blood type				
	O	**A**	**AB**	**B**	**Non-O (A, AB or B)**
Person-years	266,049	219,622	48,298	83,264	351,184
All cancers (invasive + *in situ*)					
Cases	1,284	1,136	252	435	1,823
RR (95% CI) *	1.00 (ref)	1.06 (0.98, 1.15)	1.06 (0.93, 1.22)	1.08 (0.96, 1.20)	1.07 (0.99, 1.15)
Invasive cancers					
Cases	1,040	912	212	348	1,472
RR (95% CI) *	1.00 (ref)	1.06 (0.97, 1.15)	1.10 (0.95, 1.28)	1.06 (0.94, 1.20)	1.06 (0.98, 1.15)
Ductal cancers					
Cases	792	681	146	258	1,085
RR (95% CI) *	1.00 (ref)	1.04 (0.93, 1.15)	1.00 (0.84, 1.20)	1.03 (0.90, 1.19)	1.03 (0.94, 1.13)
Lobular cancers					
Cases	121	100	28	51	179
RR (95% CI) *	1.00 (ref)	1.00 (0.77, 1.31)	1.23 (0.81, 1.85)	1.35 (0.97, 1.87)	1.12 (0.89, 1.41)
ER positive/PR positive					
Cases	614	521	119	212	852
RR (95% CI) *	1.00 (ref)	1.02 (0.91, 1.15)	1.06 (0.87, 1.29)	1.10 (0.94, 1.28)	1.05 (0.94, 1.16)
ER positive/PR negative					
Cases	144	113	26	56	195
RR (95% CI) *	1.00 (ref)	0.95 (0.74, 1.22)	0.96 (0.63, 1.46)	1.26 (0.92, 1.71)	1.02 (0.82, 1.27)
ER negative/PR negative					
Cases	131	140	30	32	202
RR (95% CI) *	1.00 (ref)	1.28 (1.00, 1.62)	1.22 (0.82, 1.82)	0.77 (0.52, 1.13)	1.15 (0.92, 1.43)
HER2/neu positive cancers					
Cases	111	105	27	37	169
RR (95% CI) *	1.00 (ref)	1.13 (0.86, 1.47)	1.32 (0.87, 2.02)	1.09 (0.75, 1.58)	1.14 (0.90, 1.46)

* Adjusted for age in months only; no evidence of confounding by any other covariate examined

Table 3

Odds ratios (OR) and 95% confidence intervals (CI) for the association between *ABO* genotype and risk of invasive breast cancer among 1,138 cases and 1,090 controls nested within the Nurses' Health Study*

	Invasive cancers	Ductal cancers	Hormone receptor positive cancers†
Genotype *O/O*			
Cases	489	394	363
Controls	471	471	471
OR (95% CI)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Genotype *A/O*			
Cases	402	327	300
Controls	369	369	369
OR (95% CI)	1.05 (0.87, 1.27)	1.06 (0.87, 1.30)	1.06 (0.86, 1.30)
Genotype *A/A*			
Cases	90	67	73
Controls	72	72	72
OR (95% CI)	1.21 (0.86, 1.69)	1.11 (0.78, 1.59)	1.33 (0.93, 1.89)
Genotype *A/B*			
Cases	48	36	42
Controls	55	55	55
OR (95% CI)	0.84 (0.56, 1.26)	0.78 (0.50, 1.21)	0.99 (0.65, 1.51)
Genotype *B/O*			
Cases	103	83	85
Controls	118	118	118
OR (95% CI)	0.84 (0.63, 1.13)	0.84 (0.62, 1.15)	0.93 (0.68, 1.27)
Genotype *B/B*			
Cases	6	6	6
Controls	5	5	5
OR (95% CI)	1.17 (0.35, 3.86)	1.47 (0.44, 4.85)	1.56 (0.47, 5.16)
Per-allele OR‡			
A^1	1.11 (0.95, 1.28)	1.10 (0.94, 1.29)	1.15 (0.98, 1.35)
A^2	0.97 (0.76, 1.23)	0.89 (0.68, 1.15)	0.98 (0.76, 1.27)
B	0.85 (0.68, 1.07)	0.85 (0.67, 1.08)	0.97 (0.77, 1.23)

*Adjusted for age in months and menopausal status at blood collection

†Estrogen receptor and/or progesterone receptor positive

‡Estimates from a single model with continuous variables for number of A^1, A^2, and *B* alleles

Table 4

Incidence rate ratios (RR) and 95% confidence intervals (CI) for the association between self-reported ABO blood type and incidence of invasive breast cancer, stratified by characteristics in 1996, among 67,697 women in the Nurses' Health Study

Characteristic in 1996	Cases	ABO blood type*				$P_{interaction}$
		O	A	AB	B	
Age (years)						
<65	1,498	1.00 (referent)	1.12 (1.00, 1.26)	1.13 (0.92, 1.37)	1.15 (0.98, 1.34)	0.29
≥65	1,014	1.00 (referent)	0.97 (0.84, 1.12)	1.05 (0.84, 1.31)	0.94 (0.77, 1.15)	
Rh factor						
Negative	510	1.00 (referent)	1.03 (0.84, 1.26)	1.06 (0.76, 1.48)	0.96 (0.73, 1.27)	0.90
Positive	1,883	1.00 (referent)	1.07 (0.97, 1.19)	1.13 (0.95, 1.35)	1.09 (0.95, 1.26)	
Menopausal status						
Pre/dubious	234	1.00 (referent)	1.33 (0.99, 1.78)	1.23 (0.71, 2.14)	1.11 (0.74, 1.67)	0.38
Post	2,274	1.00 (referent)	1.03 (0.94, 1.13)	1.08 (0.93, 1.26)	1.05 (0.92, 1.19)	
Postmenopausal hormone use						
Never	836	1.00 (referent)	1.02 (0.87, 1.19)	1.16 (0.90, 1.48)	1.05 (0.85, 1.29)	0.88
Ever	1,676	1.00 (referent)	1.08 (0.97, 1.20)	1.07 (0.89, 1.29)	1.09 (0.93, 1.26)	
BMI						
<25 kg/m2	1,042	1.00 (referent)	1.08 (0.94, 1.24)	1.20 (0.96, 1.50)	1.21 (1.01, 1.46)	0.15
25–<30 kg/m2	933	1.00 (referent)	0.97 (0.84, 1.12)	0.88 (0.68, 1.14)	0.89 (0.72, 1.09)	
≥30 kg/m2	537	1.00 (referent)	1.24 (1.02, 1.50)	1.26 (0.91, 1.74)	1.12 (0.85, 1.47)	
Smoking history						
0 pack-years	1,138	1.00 (referent)	0.95 (0.83, 1.08)	1.03 (0.82, 1.29)	0.91 (0.76, 1.10)	0.03
1–24 pack-years	787	1.00 (referent)	1.07 (0.92, 1.26)	1.06 (0.81, 1.38)	1.01 (0.81, 1.27)	
≥25 pack-years	587	1.00 (referent)	1.33 (1.10, 1.61)	1.24 (0.91, 1.69)	1.55 (1.22, 1.98)	
Family history						
No	2,041	1.00 (referent)	1.05 (0.95, 1.16)	1.11 (0.94, 1.30)	1.07 (0.94, 1.23)	0.89
Yes	471	1.00 (referent)	1.10 (0.89, 1.35)	1.13 (0.80, 1.61)	1.03 (0.76, 1.38)	

*Adjusted for age in months only

Table 5

Tumor characteristics and hazard ratios (HR) and 95% confidence intervals (CI) of death and breast cancer-specific death by self-reported ABO blood type for 2,036 invasive breast cancer cases in the Nurses' Health Study

	ABO blood type			
	O	**A**	**AB**	**B**
Tumor characteristics (%)				
Stage I	66	63	62	65
Stage II	29	33	32	29
Stage III	5	4	6	6
ER positive	84	81	82	89
PR positive	71	68	67	73
Treated with radiation	65	64	65	69
Treated with chemotherapy	38	42	37	37
Treated with tamoxifen or aromatase inhibitor	75	76	77	82
All deaths				
N	104	97	30	28
HR (95% CI) *	1.00 (referent)	1.00 (0.74, 1.34)	1.35 (0.87, 2.08)	0.81 (0.52, 1.25)
Death due to breast cancer				
N	38	42	15	12
HR (95% CI) *	1.00 (referent)	1.18 (0.72, 1.94)	1.64 (0.83, 3.24)	1.05 (0.52, 2.12)

* Adjusted for age at diagnosis (continuous), date of diagnosis (continuous), time since diagnosis (stratified), disease stage (I, II, III), radiation treatment (no/yes/missing), chemotherapy and/or hormonal therapy (neither, chemotherapy only, hormonal only, both, missing), ER/PR status (negative/positive), smoking status at diagnosis (never/past/current), BMI at diagnosis (<21, 21–<23, 23–<25, 25–<30, ≥30 kg/m^2), menopausal status and postmenopausal hormone use at diagnosis (premenopausal/dubious menopausal status, postmenopausal never user, postmenopausal past user, postmenopausal current user, missing), age at first birth and parity (nulliparous, <25 years and 1–2 births, <25 years and ≥3 births, ≥25 years and 1–2 births, ≥25 years and ≥3 births), oral contraceptive use (never/ever), physical activity after diagnosis and treatment (<2.5, 2.5–<5, 5–<10, 10–<20, 20–<30, ≥30 MET-hours/week), family history of breast cancer (no/yes)