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Cancer

The impact of hormones and reproductive factors on the risk of bladder cancer in women: results from the Nurses' Health Study and Nurses' Health Study II

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Abstract

Background: With three out of four new bladder cancer (BCa) cases occurring in men, an apparent gender disparity exists. We aimed to investigate the role of hormonal and reproductive factors in BCa risk using two large female US prospective cohorts.
Methods: Our study population comprised 118 256 and 115 383 female registered nurses who were recruited in the Nurses' Health Study (NHS) and NHS II, respectively. Reproductive and hormonal factors and other relevant data were recorded in biennial self-administered questionnaires. Cox-regression analyses were performed to estimate age- and multivariable-adjusted incidence risk ratios (IRRs) and 95% confidence intervals (CIs). Inverse-variance-weighted meta-analysis was used to pool estimates across cohorts.
Results: During up to 36 years of follow-up, 629 incident BCa cases were confirmed. In the NHS, 22 566 women (21.3%) were postmenopausal at baseline, compared with 2723 women (2.4%) in the NHS II. Among women in the NHS, younger age at menopause ($\leq$45 years) was associated with an increased risk of BCa (IRR: 1.41, 95% CI: 1.11–1.81, $P_{\text{trend}} = 0.01$) compared with those with menopause onset at age 50+ years, particularly

among ever-smokers (IRR for age at menopause $\leq$45 years: 1.53, 95% CI: 1.15–2.04; $P_{\text{Intx}} = 0.16$). Age at menarche and first birth, parity, oral-contraceptive use and postmenopausal hormone use were not associated with BCa risk.

Conclusions: Overall, we found little support for an association between female reproductive factors and BCa risk in these prospective cohort studies. Earlier age at menopause was associated with a higher risk of BCa, particularly among smokers, indicating the potential for residual confounding.

Key words: Bladder cancer, hormones, reproductive factors, females, Nurses' Health Study

Key Messages

- Women who experience earlier age at menopause have a higher risk of bladder cancer; this risk is restricted primarily to women with a smoking history.
- Age at menarche, parity and contraceptive use are not associated with bladder cancer risk.
- Female sex hormones appear to have little importance in regard to bladder cancer risk.

Introduction

Bladder cancer (BCa) is the ninth most commonly diagnosed cancer worldwide.[1] In the USA alone, the estimated numbers of new BCa cases in 2018 in men and women were 62 380 and 18 810, with estimated death rates of 20% and 25%, respectively.[2] Despite the strong male predominance in incidence, women are more likely to be diagnosed with more advanced disease and may face worse survival.[3–5] Smoking and occupational exposures, particularly exposure to aromatic amines such as rubber, plastic and dye, are the strongest risk factors for BCa.[6] Despite the higher prevalence of smoking among men, differences in smoking patterns and even occupational exposures do not fully explain discrepancies in incidence or prognosis of BCa between men and women.[6–8] A salient factor that might provide a reasonable explanation is differences in the hormonal milieu in women, compared with men—particularly the use of exogenous hormones, as well as menopausal hormone changes.

Current evidence from mice models and human-cell preclinical studies suggests that sex steroid hormones and their receptors might play a role in BCa pathogenesis and disease progression.[9] Oestrogen appears to inhibit tumour initiation but paradoxically enhances disease progression.[10] There is a growing body of literature suggesting a possible association between the expression of steroid receptors in bladder specimens and clinicopathological features, as well as BCa prognosis.[11] Nevertheless, the exact up/downregulation pattern and its association with clinicopathological features and BCa risk are as yet unclear.

Several epidemiological studies have evaluated the impact of reproductive and hormonal factors on the risk of BCa,[12–15] with inconsistent results. Understanding the effects of hormonal and reproductive factors on BCa risk could help in early detection, potentially improving treatment outcome. Twelve years ago, we carried out an analysis on this association in the Nurses' Health Study (NHS), showing that menopausal status and age at menopause may play a role in modifying BCa risk in women.[12] With 10 years of additional follow-up and double the number of cases from the same and another US cohort, we sought to re-evaluate the effect of hormonal and reproductive factors on BCa risk to provide a more definitive conclusion.

Methods

Study cohorts

This study relied on the NHS and NHS II, two ongoing prospective cohort studies established in 1976 and 1989, respectively. The NHS enrolled 121 701 female registered nurses between the ages of 30 and 55 years, whereas the NHS II recruited 116 428 female registered nurses between the ages of 25 and 42 years. In both cohorts, all participants completed a baseline questionnaire assessing height, weight, health-related information, medical history, smoking status, history of cigarette smoking, physical activity, reproductive history, use of exogenous hormones and diet, with biennial updates on subsequent questionnaires (except for diet, which is updated every 4 years).

We excluded women with missing birth date (151 in the NHS and none in the NHS II) and women who died before baseline or were diagnosed with cancer (3294 in the NHS and 1045 in the NHS II, except non-melanoma skin cancer). The cohort for analysis consisted of 233 639 women: 118 256 from the NHS and 115 383 from the NHS II. As of 2012, the overall response rate for participants in both cohorts was >85%.[16] We determined vital status through next of kin and the National Death Index, with a >98% confirmation rate of all deaths in the cohorts.[17] This study was approved by the institutional review board of the Brigham and Women's Hospital, Boston, Massachusetts.

Assessments of reproductive factors and exogenous hormone use

Menopausal status and age at onset of menopause were first determined from initial questionnaires in 1976 and 1989, and subsequently updated on each biennial questionnaire. The questionnaires queried whether the participant's menstrual periods had ceased permanently and, if so, at what age and for what reason (e.g. natural, surgical, radiation). If menopause was due to surgery, the participant was asked to report the number of ovaries removed.

Women were defined as postmenopausal from the self-reported time of natural menopause or hysterectomy with bilateral oophorectomy (i.e. surgical menopause). If a woman underwent hysterectomy without bilateral oophorectomy, she was classified as postmenopausal once she reached the age at which 90% of the NHS cohort went through menopause (54 years for smokers and 56 years for non-smokers). In the NHS, a nurse's self-reports of age at menopause[18] and type of menopause[19] were both found to be highly accurate.

Use and duration of hormone replacement therapy (HRT) were first determined on the baseline questionnaire, and information on type of HRT use was subsequently updated biennially. Each biennial questionnaire ascertained whether a participant was using HRT (within the past month) and the number of months for which HRT had been used during the past 24 months since the last biennial questionnaire was completed. Women with missing data on HRT use for a given 2-year period were assigned to the missing category for that time period. We enquired about pregnancy and number of live births from baseline until the end of reproduction in both cohorts, recording parity as the total number of live births. In addition, participants responded to questions about their age at menarche and provided updated information on the duration of oral-contraceptive use. We classified women as ever- or never-users of oral contraceptives and computed their total duration of use in months.[20]

Assessment of smoking status

On each questionnaire, current smokers reported the average number of cigarettes smoked per day. We categorized participants' cigarette-smoking history as 'current', 'former' or 'never'-smoker at each time interval. When a nurse did not report smoking habits for a given period, we carried forward the information from the previous questionnaire, until a report was available again. In addition, we computed the cumulative total number of pack-years of smoking among ever-smokers by multiplying the average reported number of packs smoked per day by the number of years of smoking in each time period, summing up over all previous time periods.[20]

Ascertainment of bladder cancer diagnosis

On each biennial questionnaire, participants were asked to report any disease or medical condition that had been diagnosed during the previous 2-year period. Whenever a participant reported a diagnosis of BCa, we asked for permission to obtain related medical records. If permission to obtain records was denied, we attempted to confirm the self-reported cancer with an additional letter or telephone call to the participant. If the primary cause of death listed on a death certificate was previously unreported BCa, we contacted a family member (subject to state regulations) to obtain permission to retrieve medical records or to confirm a diagnosis of BCa. Hospital records and pathology reports that were obtained were reviewed by trained physicians, blinded to exposure information. Overall, we were able to confirm about 95% of self-reported cases of BCa; 85% of self-reported cases of BCa were confirmed by medical-record review with a >98% confirmation rate of all deaths in the cohorts.[17] Because of the high accuracy of self-reported disease outcomes in this cohort,[16] we included cases for which we were unable to obtain medical records.

Statistical analyses

Person-time of follow-up was calculated for each participant from the return date of the baseline questionnaire to the date of BCa diagnosis, death from any cause or the end of follow-up (1 June 2012 in the NHS for a total of 36 years of follow-up; and June 2013 in the NHS II for a total of 24 years of follow-up), whichever occurred first. Those who reported any cancer (with the exception of non-melanoma skin cancer), or with missing information on the primary exposure variable, were excluded from subsequent follow-up; therefore, slightly different numbers of women contribute to each analysis. Incidence rates of BCa were computed by dividing the number of incident cases by the number of person-years in each category of exposure.

Time-varying Cox proportional-hazards models, using study period as the time scale, were used to estimate multivariable incidence rate ratios (IRRs) and 95% confidence intervals (CIs), adjusting simultaneously for age (in months) and additional confounding variables. Categories for the exposure variables and confounding factors were selected for consistency and comparability with previous analyses in this cohort and with prior published literature.[12] Given the small number of postmenopausal women in the NHS II (2.4%), the association between menopause status and BCa was only assessed in the NHS. We analysed menopausal status (pre- vs postmenopausal), age at menopause ($\leq$45, 45 < age < 50, and $\geq$50 years), type of menopause (natural vs surgical menopause) and menopausal hormone use (any, oestrogen, and oestrogen and progestin: never, past, current <2, 2–4, 5–9 and $\geq$10 years). In both cohorts, reproductive exposures included: age at menarche (<12, 12, 13 and $\geq$14 years), oral-contraceptive use (never-user, ever-user 1–2 years and ever-user $\geq$3 years), parity (nulliparous, one child, two children, three or four children and five or more children) and a combination of parity and age at first birth (nulliparous, one or two children at age $\leq$24 years, one or two children at age 25–29 years, one or two children at $\geq$30 years, at least three children age at $\leq$24 years and at least three children at age $\geq$25 years). We have adjusted for most known BCa risk factors in the final multivariable models: age, 2-year questionnaire period, body mass index (<21, 21–22.9, 23–24.9, 25–29.9 and $\geq$30 kg/m^2), cigarette-smoking status (never, former, current), pack-years of cigarette smoking (as a continuous variable) and cumulative total fluid intake (quartiles). In secondary analysis, we also adjusted for spousal- and parental-smoking history, but results remained essentially unchanged and, therefore, we did not retain these variables in our final models.

Tests for multiplicative interaction were performed by examining stratum-specific results for smoking and tested formally by using likelihood ratio tests comparing the model having both the main effects and the interaction terms with the model having the main effects only. Tests for linear trend were conducted by using the group number of the exposure category as an integer variable. Inverse-variance-weighted meta-analysis was used to pool estimates across cohorts. All the statistical procedures were performed with SAS software Version 9.4 (SAS Institute, Inc., Cary, NC). All *P*-values are based on two-sided tests.

Results

We identified 629 incident BCa cases (575 in the NHS and 54 in the NHS II) between 1976 and 2012. At baseline, the mean age at menopause of women in the NHS was 50.4 vs 38.5 years among the NHS II participants. By design, women in the NHS II were younger than in the NHS; therefore, postmenopausal women in the NHS II represented only a small percentage of the study population at baseline, compared with the NHS (21.3% vs 2.4%). Moreover, participants of the NHS II tended to have used oral contraceptives more frequently (83.1% vs 55% in premenopausal women) and were less likely to smoke than women in the NHS. Table 1 summarizes the baseline age-adjusted characteristics stratified by menopausal status in the NHS and NHS II.

Table 2 shows the association between postmenopausal factors in women in the NHS and BCa risk. We excluded participants of the NHS II from this analysis because of low case numbers and the very low proportion of postmenopausal women. Age at onset of menopause of $\leq$45 years (vs $\geq$50 years) was associated with a higher risk of BCa in the age-adjusted (IRR: 1.59, 95% CI: 1.24–2.03, $P_{\text{trend}} = 0.0004$) and multivariable-adjusted (IRR: 1.41, 95% CI: 1.11–1.81, $P_{\text{trend}} = 0.01$) models. Conversely, type of menopause (surgical vs natural; IRR: 1.11, 95% CI: 0.87–1.41) and menopausal hormone use (ever-use vs never-use; IRR: 1.12, 95% CI: 0.92–1.38) were not associated with BCa risk in the multivariable-adjusted model. Similarly, analyses addressing oestrogen alone or oestrogen plus progestin as separate variables did not reveal associations with BCa risk.

We also assessed the association between premenopausal hormonal factors and BCa risk in both cohorts. Age of menarche, age at first birth, parity and oral-contraceptive use were not associated with an increased risk of BCa in both cohorts. Table 3 shows the age-adjusted and multivariable-adjusted IRR in the NHSI and NHS II, as well as the meta-analysed results of both cohorts, which did not materially change these results. Overall, none of the reproductive factors examined was associated with BCa risk. For example, the meta-analysed multivariate-adjusted IRR for age at menarche ($\geq$14 vs <12 years) and oral-contraceptive ever-use ($\geq$3 years vs never-user) were 1.09 (95% CI: 0.80–1.49) and 0.86 (95% CI: 0.62–1.21), respectively.

In secondary analyses, we stratified by smoking status (Table 4). Overall, the association between age at menopause and BCa risk did not vary significantly by smoking status ($P_{\text{intx}} = 0.164$). However, BCa risk was higher among women who experienced an early menopause (i.e. at age $\leq$45 years, compared with women age >50 years at menopause) if they reported a smoking history (IRR: 1.53, 95% CI: 1.15–2.04) vs if they had never smoked (IRR: 1.12, 95% CI: 0.67–1.86).

Discussion

In this large, prospective cohort of US nurses and with 36 years of follow-up, we found that women who

Table 1. Age and age-adjusted baseline characteristics by menopausal status of 116 586 women in the US Nurses' Health Study (NHS) and 114 671 women in the US Nurses' Health Study 2 (NHS II)[ab]

Characteristics	NHS		NHS II	
	Menopausal status			
	Premenopausal	Postmenopausal	Premenopausal	Postmenopausal
No. of participants (%)	83 571 (78.7)	22 547 (21.3)	111 251 (97.6)	2723 (2.4)
Age[c] (years)	40.3 (6.1)	50.5 (4.5)	34.7 (4.6)	38.5 (3.7)
Body mass index (kg/m^2)	23.6 (4.1)	24.4 (4.3)	24.1 (5.0)	25.5 (5.9)
Cigarette-smoking status (%)				
Never	44.9	40.8	65.8	58.1
Past	23.5	21.4	21.2	22.1
Current	31.7	37.8	13.0	19.8
No. of pack-years of smoking[d]	16.4 (13.3)	25.7 (17.6)	11.3 (8.1)	15.3 (9.7)
Age at menarche (years)	12.5 (1.4)	12.7 (1.5)	13.4 (1.5)	13.2 (1.6)
Parous (%)	92.5	88.2	69.7	68.5
Age at first birth (years)[e]	24.9 (3.2)	26.1 (3.8)	25.5 (4.0)	23.4 (3.9)
Parity[e]	3.1 (1.5)	3.2 (1.6)	2.1 (0.9)	2.0 (0.8)
Ever oral-contraceptive use (%)	55.0	24.4	83.1	89.8
Total fluid intake[f] (mL)	2015.0 (742.5)	2053.7 (728.7)	2153.2 (858.5)	2244.6 (891.6)
Natural menopause[g] (%)	–	63.7	–	17.8
Age at natural menopause (years)	–	47.9 (4.1)	–	33.8 (6.7)
Menopausal hormone use (%)				
Never	6.7	44.9	2.6	7.5
Past	0.9	17.7	0.5	8.6
Current	0.6	33.7	0.4	83.3
Duration of menopausal hormone use (months)	7.9 (24.0)	24.4 (40.9)	21.5 (129.1)	92.2 (220.7)

[a]Baseline numbers reflect all women for whom menopausal status was available at baseline.
[b]All data reported as either percentage or mean (standard deviation). Values may not add to 100% because of missing data.
[c]Not age-adjusted.
[d]Among cigarette smokers.
[e]Among parous women.
[f]Fluid-intake information assessed in 1989.
[g]Among postmenopausal women.

experienced menopause at age ≤45 years had significantly higher risk of BCa compared with women with an older menopause age (≥50 years). This association was strongest among the subgroup of women who had ever smoked. Other reproductive and hormonal factors such as age at menarche, parity and oral-contraceptive as well as post-menopausal hormone use were not associated with BCa risk. These findings were consistent across the two cohorts. We confirm our previous findings by McGrath *et al.*[12] in 2006 and provide new evidence to support a protective impact of longer reproductive time (≥40 vs ≤35 years) on BCa risk in this updated cohort analysis with longer follow-up duration and twice as many BCa cases. Moreover, we also did not find an association between pre-menopausal reproductive and hormonal factors and BCa risk in participants from the NHS and NHS II.

Prizment *et al.*[15] found in the Iowa Women's Health study that earlier age at menopause is associated with an increased risk of BCa. Similarly to our results, they found that this association is slightly stronger in smokers but not among non-smokers. On the other hand, one case–control study that included 152 women with BCa and 166 controls reported no association with menopausal age, age at menarche or age at first birth.[21] The authors reported only a protective effect in ever-parous women in comparison to never-parous women. This study has several limitations including the case–control design, sample size and lack of detailed information on risk factors, with a significant proportion of missing data. One large population-based study from Sweden showed that older age of menarche and parity lowered the risk of BCa.[22] Nevertheless, this study also suffered from several shortcomings, including lack of information on cigarette smoking and detailed reproductive history (data on menstrual history and use of exogenous hormones were absent). Conversely, we found that the use of menopausal hormones, oral contraception, age at menarche or age at first birth were not associated with the risk of developing BCa. These results reconcile with all

Table 2. Associations of hormonal factors and bladder cancer risk among 116 586 women in the US Nurses' Health Study (1976–2012)

Factor	No. of cases	No. of person-years of observation	Age-adjusted IRR[a]	95% CI[a]	Multivariate-adjusted IRR[b]	95% CI
Age (years) at menopause[c]						
$\geq$50	188	797 746	1 (ref)		1 (ref)	
45 < age < 50	90	360 407	1.24	0.98, 1.57	1.09	0.86, 1.38
$\leq$45	50	146 574	1.59	1.24, 2.03	1.41	1.11, 1.81
			$P_{trend} = 0.0004$		$P_{trend} = 0.0120$	
Natural menopause	328	1 321 490	1 (ref)		1 (ref)	
Surgical menopause	87	391 625	1.01	0.80, 1.29	1.11	0.87, 1.41
Any menopausal hormone						
Never-use	141	743 410	1 (ref)		1 (ref)	
Current use	122	686 271	0.85	0.66, 1.09	0.95	0.74, 1.22
Ever-use	342	1 356 905	1.06	0.87, 1.30	1.12	0.92, 1.38
User, <2 years	69	275 474	1.21	0.90, 1.61	1.19	0.89, 1.60
User, $\geq$2 but <5 years	60	312 468	0.7	0.71, 1.31	1.02	0.75, 1.35
User, $\geq$5 but <10 years	79	326 450	1.06	0.80, 1.40	1.13	0.85, 1.50
User, >10 years	134	441 512	1.04	0.81, 1.33	1.14	0.89, 1.46
			$P_{trend} = 0.90$		$P_{trend} = 0.39$	
Oestrogen use						
Never-use	292	1 255 867	1 (ref)		1 (ref)	
User, <2 years	35	123 653	1.20	0.84, 1.70	1.19	0.84, 1.70
User, $\geq$2 but <5 years	41	176 695	0.99	0.71, 1.38	1.03	0.74, 1.43
User, $\geq$5 but <10 years	39	141 948	1.13	0.81, 1.59	1.20	0.85, 1.67
User, >10 years	58	187 262	1.06	0.80, 1.41	1.13	0.85, 1.51
			$p_{trend} = 0.53$		$p_{trend} = 0.27$	
Oestrogen and progestin use						
Never-use	352	1 440 370	1 (ref)		1 (ref)	
User, <2 years	29	104 680	1.06	0.72, 1.55	1.09	0.74, 1.60
User, $\geq$2 but <5 years	35	180 496	0.73	0.51, 1.04	0.76	0.53, 1.08
User, $\geq$5 but <10 years	27	105 399	0.85	0.57, 1.26	0.88	0.59, 1.32
User, >10 years	22	54 480	1.17	0.75, 1.83	1.23	0.79, 1.91
			$P_{trend} = 0.38$		$P_{trend} = 0.59$	

[a]IRR, incidence rate ratio; CI, confidence interval.

[b]Adjusted for age (months), time period (2-year questionnaire period), smoking status (never, former, current) and pack-years of smoking (continuous), body mass index (<21, 21–22.9, 23–24.9, 25–29.9, $\geq$30 kg/m^2) and cumulative total fluid intake (quartiles).

[c]This analysis was conducted amongst 78 134 postmenopausal women only. Age at menopause amongst women who experienced a natural menopause.

previously published studies.[12,14,15] It is worth noting that Cantwell *et al.*[14] did not find an association between age of menopause and BCa risk. However, the relatively shorter follow-up duration and rather low case number preclude drawing definitive conclusions in light of conflicting results in the literature.

The fluctuation of the hormonal milieu during a woman's lifetime and underlying downstream molecular mechanism provide an appealing theory behind the paradoxical findings regarding BCa incidence between the sexes.[8] Late age at menarche[13] and earlier age of menopause[12] may imply lower cumulative exposure to hormonal stimulation during a woman's lifetime, explaining the gender gap in incidence. This phenomenon has been explained by several other hypotheses, such as their lower incidence of smoking and occupational exposures to aromatic amines and polycyclic aromatic hydrocarbons, as well as delayed access to health care and delay in seeking medical advice, resulting in delayed diagnosis.[8,23]

Strengths of our study include the use of two large prospective studies with long follow-up and high response rates. To our knowledge, this is the largest study available in the literature that investigated the role of hormonal factors on the development of BCa in women with detailed data on hormonal and reproductive factors, as well as smoking history. Our study is not devoid of limitations. First, despite the prospective nature of the NHS and NHS II, we cannot exclude the possibility of residual confounding by factors that may have influenced the association of reproductive factors and BCa, such as smoking

Table 3. Association of hormonal factors and bladder cancer risk among 116 586 women in the US Nurses' Health Study (NHS) (1976–2012) and 114 671 women in the US Nurses' Health Study 2 (NHS II) (1989–2013)

Factor	NHS					NHS II					Meta-analysed results		
	No. of cases	Age-adjusted IRR[a]	95% CI[a]	Multivariate-adjusted IRR[b]	95% CI	No. of cases	Age-adjusted IRR[a]	95% CI[a]	Multivariate-adjusted IRR[b]	95% CI	Multivariate-adjusted IRR	95% CI	pHet
Age at menarche (years)													
<12 years	119	1 (ref)		1 (ref)		13	1 (ref)		1 (ref)		1 (ref)		
12 years	173	1.21	0.96, 1.53	1.24	0.98, 1.57	13	0.79	0.36, 1.71	0.83	0.38, 1.81	1.20	0.96, 1.50	0.34
13 years	169	1.00	0.79, 1.27	1.05	0.83, 1.33	14	0.94	0.44, 2.01	1.02	0.47, 2.19	1.04	0.83, 1.31	0.95
≥14 years	114	0.97	0.75, 1.25	1.02	0.79, 1.32	13	1.42	0.66, 3.08	1.60	0.73, 3.50	1.09	0.80, 1.49	0.29
Oral-contraceptive use													
Never-user	421	1 (ref)		1 (ref)		17	1 (ref)		1 (ref)		1 (ref)		
Ever-user, 1–2 years	40	0.75	0.53, 1.04	0.73	0.52, 1.02	14	1.20	0.59, 2.43	1.15	0.56, 2.34	0.82	0.56, 1.19	0.27
Ever-user ≥3 years	110	0.99	0.79, 1.23	0.94	0.75, 1.17	17	0.65	0.33, 1.28	0.61	0.31, 1.21	0.86	0.62, 1.21	0.24
Parity combined with age at first birth (years)													
Nulliparous	40	1 (ref)		1 (ref)		12	1 (ref)		1 (ref)		1 (ref)		
1 or 2 children ≤24 years	71	0.81	0.55, 1.20	0.79	0.53, 1.17	8	0.68	0.27, 1.67	0.63	0.26, 1.57	0.76	0.53, 1.09	0.66
25–29 years	100	1.00	0.69, 1.45	1.02	0.71, 1.48	8	0.60	0.25, 1.47	0.64	0.26, 1.56	0.95	0.68, 1.34	0.34
≥30 years	40	0.81	0.52, 1.27	0.84	0.54, 1.31	7	0.75	0.29, 1.98	0.77	0.30, 1.97	0.83	0.55, 1.23	0.87
3 or more children ≤24 years	189	0.77	0.54, 1.08	0.75	0.53, 1.06	12	1.33	0.59, 2.98	1.30	0.58, 2.92	0.87	0.54, 1.40	0.22
≥25 years	131	0.70	0.49, 1.00	0.71	0.50, 1.01	7	0.84	0.33, 2.14	0.87	0.34, 2.24	0.73	0.52, 1.02	0.69
Parity													
Nulliparous	40	1 (ref)		1 (ref)		12	1 (ref)		1 (ref)		1 (ref)		
1 child	49	0.96	0.63, 1.47	0.99	0.65, 1.50	1	0.10	0.01, 0.78	0.10	0.01, 0.76	0.39	0.04, 3.45	0.03
2 children	162	0.87	0.61, 1.23	0.87	0.61, 1.23	22	0.90	0.44, 1.81	0.91	0.45, 1.85	0.88	0.64, 1.20	0.90
3 or 4 children	226	0.71	0.50, 0.99	0.71	0.50, 0.99	19	1.16	0.56, 2.41	1.17	0.56, 2.43	0.82	0.52, 1.27	0.22
5 or more children	94	0.82	0.57, 1.19	0.81	0.55, 1.17	0	–	–	–	–	–	–	–

[a]IRR, incidence rate ratio; CI, confidence interval.

[b]Adjusted for age (months), time period (2-year questionnaire period), smoking status (never, former, current) and pack-years of smoking (continuous), body mass index (<21, 21–22.9, 23–24.9, 25–29.9, ≥30 kg/m^2) and cumulative total fluid intake (quartiles).

Table 4. Association of age at menopause and bladder cancer risk among 116 586 women in the US Nurses' Health Study according to smoking status

Factor	No. of cases	Age-adjusted IRR[a]	95% CI[a]	Multivariate-adjusted IRR[b]	95% CI
Age of menopause (never-smokers)					
≥50 years	69	1 (ref)		1 (ref)	
>45 years but < 50 years	20	0.68	0.38, 1.23	0.71	0.39, 1.27
≤45 years	22	0.84	0.36, 1.98	0.82	0.34, 1.97
Age of menopause (ever-smokers)					
≥50 years	131	1 (ref)		1 (ref)	
>45 years but < 50 years	93	1.34	1.00, 1.79	1.19	0.89, 1.59
≤45 years	80	1.94	1.37, 2.76	1.66	1.16, 2.36
			p for interaction: 0.164		

[a]IRR, incidence rate ratio; CI, confidence interval.
[b]Adjusted for age (months), time period (2-year questionnaire period), smoking status (never, former, current) and pack-years of smoking (continuous), body mass index (<21, 21–22.9, 23–24.9, 25–29.9, ≥30 kg/m^2) and cumulative total fluid intake (quartiles).

dose. However, residual confounding is likely considerably smaller than in most prior studies, given the detailed and repeated assessments of smoking exposure. Consequently, our results support future research efforts to focus on other potential mechanisms, such as differences in metabolic detoxification of carcinogens, to explain the gender gap in BCa.[24] Due to the absence of survival data among BCa cases in our cohorts and the lack of male participants, we are unable to evaluate the effect of hormonal and reproductive history on BCa survival or explore sex differences. Further, whereas some factors, such as access to health care and the working environment, were not assessed in detail, women in these cohorts, all of whom were nurses working in the USA, are presumed to have easier access to health care.[25,26] Second, the number of participants in the NHS II who were postmenopausal or developed BCa was substantially lower due to their younger age. Although this limited our ability to investigate age at menopause and BCa in NHS II, results for the association between premenopausal hormonal and reproductive factors and BCa risk were similar in both cohorts. In fact, the inclusion of a large cohort of younger women (NHS II) provided a level of comparability for premenopausal reproductive and hormonal factors, and strengthened our conclusions.

Conclusion

Whereas we observed that women who experienced earlier age of menopause (i.e. presumably with lower cumulative exposure to female sex hormones) had a higher risk of BCa, this risk was restricted primarily to women with a smoking history, indicating the potential for residual confounding. Therefore, the inhibitory role for female sex hormones on BCa risk appears to have little importance. Further efforts should be undertaken to evaluate other potential pathways to explain the existing gender gap in BCa.

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Conflict of interest: E.D. has received consulting fees from Epi Excellence and Bohn Epidemiology. E.S. serves on the scientific advisory board for the Houska award. S.F.S. is an advisory board member of Astellas, Cepheid, Ipsen, Ferring, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanofi, and Wolff, and is speaker for Astellas, Ipsen, Ferring, Jansen, Lilly, Olympus, Pfizer, Pierre Fabre, Sanochemia, Sanofi, and Wolff. The other authors declare that they have no competing conflict of interest. The authors alone are responsible for the content and writing of the paper.

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