Published in final edited form as:
Int J Cancer. 2013 July 15; 133(2): 462–472. doi:10.1002/ijc.28022.

Reproductive factors and menopausal hormone therapy and bladder cancer risk in the NIH-AARP Diet and Health Study

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Abstract

The incidence of bladder cancer among women is at least one third to one fourth that observed among men in many countries. Even after accounting for known risk factors, the reason for this gender disparity remains unexplained. We conducted a comprehensive evaluation of reproductive factors and exogenous hormone use with a primary focus on menopausal hormone therapy use and risk of bladder cancer in women in the NIH-AARP Diet and Health Study. Reproductive and hormonal factors were ascertained on the baseline questionnaire in 1995–1996 among 201,492 females who were followed until December 31, 2006. During follow-up, 651 cases of bladder cancer were diagnosed. A subset of women provided detailed information on use of MHT in a second questionnaire in 1996–1997. In this analysis, 127,361 females were followed through June 30, 2002 and 198 incident bladder cancer cases were identified. Cox proportional hazard models, adjusted for smoking status, cigarettes per day, and body mass index using age as the time metric, were used to obtain hazard ratios (HRs). A reduced risk was observed among parous women (HR=0.76; 95% CI 0.62–0.93) and women who reported late age at menarche (≥15 years) (HR=0.57; 95% CI 0.39–0.84). Women who reported ever using estrogen and progestin therapy had a decreased risk (HR=0.53; 95% CI: 0.34–0.83) compared to women who did not report MHT use. No association was observed for estrogen only users (HR=0.82; 95% CI: 0.58–1.15). Our results suggest a putative role for sex hormones in the etiology of bladder cancer among women.

Keywords

reproductive factors; estrogen; progestin; parity; bladder cancer

INTRODUCTION

Men have a 3- to 4- fold greater risk for bladder cancer than women (1). Even after accounting for known risk factors such as cigarette smoking and occupation, the explanation for the excess bladder cancer in men compared to women living in the United States remains unresolved (2). Sex steroid hormones have been shown to modify the development and progression of chemically induced bladder cancer in animal models, with estrogen inhibiting

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or delaying progression and androgen potentiating bladder carcinogenesis(3–6). While these experimental findings suggest that hormonal differences may account for part of the gender disparity in humans, the importance of estrogen and progesterone in the development of bladder carcinogenesis in women remains to be determined.

Several hormonal and reproductive factors have been shown to be associated with bladder cancer risk in women. Two recent meta-analyses of four cohort and five case-control studies reported a 30% reduction in risk for bladder cancer among parous women (7;8) and one meta-analysis reported a significantly elevated risk associated with early age at menopause (8).

The association between bladder cancer and exogenous hormone use, including menopausal hormone therapy (MHT), is less clear. Several case-control and cohort studies have evaluated MHT and bladder cancer risk and found either no association (9;10) or an elevated association (8;11;12) with a recent meta-analysis reporting evidence of heterogeneity (8). Three prospective cohort studies, however, have reported differences in bladder cancer risk by MHT formulation. Combined estrogen and progestin therapy was associated with a 30–40% reduction in risk of bladder cancer (7;13;14), although only one study was statistically significant (7). No association was found with estrogen use alone (7;13;14). Additional research in a large prospective cohort study is needed to evaluate significant differences in risk of bladder cancer by MHT formulation.

We conducted a comprehensive evaluation of hormonal and reproductive factors with a primary focus on MHT use and risk of bladder cancer in the NIH-AARP Diet and Health Study. This large prospective cohort study ascertained MHT use including questions related to formulation, regimen, duration, and recency of use prior to the release of the findings from the Women's Health Initiative showing the health effects of estrogen and progestin (15). In addition, we stratified our MHT analysis by hysterectomy status, since general practice guidelines recommend that estrogen be combined with progestin for women who have an intact uterus in order to avoid endometrial hyperplasia (21). This analysis is the largest prospective investigation of reproductive factors and bladder cancer risk, with a detailed evaluation of MHT use and bladder cancer risk.

MATERIALS AND METHODS

Study Design

The NIH-AARP Diet and Health Study is a prospective cohort study of diet and lifestyle factors initiated in 1995–1996. A baseline questionnaire was sent to 3.5 million AARP members (50–71 years old) from six US states (CA, FL, LA, NJ, NC, PA) and two metropolitan areas (Atlanta, GA and Detroit, MI) and was returned by 617,119 individuals (17.6%), of which 566,399 were considered eligible (16). Exclusions were applied to those who had questionnaires filled out by proxies (n=15,760), were male (n=325,172), or had a previous cancer diagnosis (n=23,957), leaving a final baseline study population of 201,492 women. A second questionnaire, which ascertained details of MHT use, was sent in 1996–1997 to participants who did not have self-reported colon, breast or prostate cancer at baseline and was completed by 334,906 individuals (62% of those eligible at baseline). Individuals were excluded if the questionnaire was filled out by proxies (n=10,383), were male (n=188,116), or had a previous cancer diagnosis (n=9036), leaving 127,361 women for the second questionnaire population. A third questionnaire was sent out to all living participants in 2004–2006 and 91,140 women who had completed both the 1996–1997 and 2004 questionnaire (67.6% of 134,842 women on the second questionnaire) were identified for a sensitivity analysis.

Assessment of Reproductive factors

Age at menarche, duration of oral contraceptive use, number of live-born children, age at first birth, age at menopause, reason for menopause, hysterectomy status, oopherectomy status, and menopausal hormone therapy use were ascertained on the baseline questionnaire. Demographics, body mass index, smoking status and frequency of cigarette use, and race were also captured on the baseline questionnaire.

The second questionnaire collected additional information on lifestyle factors, body mass index at earlier ages, and more detailed information on MHT use. Detailed information on oral MHT use was ascertained, including ever use, first and last date of use, duration of use measured in years, frequency of use, and regimen followed. Estrogen pill use and progesterone/progestin pill use was assessed separately on the 1996–1997 questionnaire, as the first combined pill of estrogen and progestin was not marketed until 1995 (17).

Separate exposure categories for various formulations of estrogen and progestin use were created based on reported duration and start and stop dates (18). Due to similar parameter estimates or small numbers, all estrogen and progestin (EPT) users with known duration were combined into one exposure category for the main analyses. Women with unknown duration of either estrogen or progestin were not included in any combined EPT estimate.

A sequential regimen was defined as combined EPT use for fewer than 15 days per cycle. Continuous estrogen plus progestin regimens were defined as combined estrogen and progestin use for 15 or more days per cycle.

Bladder cancer ascertainment

Incident cases of primary carcinoma of the urinary bladder including carcinoma *in situ* (ICD-0-3:C670-679) were ascertained by record linkage to state cancer registries. The validation study of cancer ascertainment has shown a high level of ascertainment of incident cancer cases (≥90%) from cancer registries (19). Cohort participants were followed on an annual basis for change of address by matching cohort participants with the National Change of Address database maintained by the U.S. Postal Service. Vital status was ascertained through periodic linkage of the cohort to the Social Security Administration (SSA) Death Master File in the United States, follow-up searches of the National Death Index Plus for participants matched to the SSA Death Master File, cancer registry linkage, questionnaire responses, and responses to other mailings.

Statistical Methods

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for the association of hormonal and reproductive factors and risk of bladder cancer using Cox proportional hazards models with age as the time metric. Follow-up time started at the age at baseline questionnaire for all reproductive and hormonal factors except MHT, and ended at the age of bladder cancer diagnosis or age at censoring. Censoring events were diagnosis of any other cancer, death, date when individual moved out of cancer ascertainment area, or end of study (December 31, 2006), whichever occurred first. When estimating HRs for MHT, follow-up time started at age of the 1996–1997 questionnaire and censoring ended for all women on June 30, 2002, a date just prior to the publication of the WHI report on the health effects of MHT(15). The WHI findings caused rapid and widespread cessation of MHT use after July 2002, increasing the likelihood that the MHT use reported by participants on the 1996–1997 questionnaire was not valid after July 2002.

Models were adjusted for smoking status and number of cigarettes smoked per day (never smoker, former 1–20 cigarettes/day, former 21–40 cigarettes/day, former 41+ cigarettes/day,

current 1–20 cigarettes/day, current 21–40 cigarettes/day, current 41+ cigarettes/day), as well as body mass index (18.5-<25 kg/m^2, 25-<30 kg/m^2, >=30 kg/m^2, unclassifiable). Additional factors including education and race were also evaluated in the multivariate models, but did not significantly alter the estimates, so they were not included in the final models. Indicator variables were created for missing values, where appropriate. No variable was missing more than 5% of the data. Linear trends of bladder cancer risk with increasing frequency of exposure were evaluated using the Wald chi-square test for the trend variable.

Because the 2004–2006 questionnaire also collected data on MHT use, we conducted a sensitivity analysis based on a time-varying covariate for MHT recency and duration (separately for estrogen only use and combined estrogen and progestin use) among the 91,140 women who completed the 1996–1997 and 2004 questionnaires. To allow for a comparison with the main analysis, follow-up time for the sensitivity analyses continued until June 30, 2002, with identical censoring as described above.

To evaluate the impact of differences in the women who had responded to the different questionnaires, we tested for heterogeneity in parameter estimates for MHT use reported on the 1996–1997 questionnaire among women from the 1996–1997 questionnaire compared to the subset of women who had completed both the 1996–1997 and 2004–2006 questionnaire using a 2 df of freedom heterogeneity test. A robust sandwich estimate for the covariance matrix was applied to account for the correlations between repeated observations in the two samples.

Risk estimates were calculated overall, and stratified by smoking status because of its known anti-estrogenic effects (20), by body mass index which serves as an important source of estrogen for postmenopausal women, and by hysterectomy status at baseline due to the specific guidelines for MHT formulation use based on hysterectomy status (21). For MHT, we present the most clinically relevant subgroup by hysterectomy status in the tables. Heterogeneity across strata was assessed by the likelihood ratio test comparing models with and without the corresponding interaction term. When we assessed urothelial transitional cell carcinomas (ICD-O-3 8120, 8120/3, 8122, 8130, 8130/2, 8130/3) (n=188), individuals diagnosed with other bladder tumors contributed follow-up time as non-cases until their diagnosis.

We performed a meta-analysis including hazard ratios from our study and the three other studies to date that have evaluated bladder cancer risk in relation to estrogen and progestin use separately from estrogen use only (7;13;14). Study-specific HRs were combined using fixed effects and random effects meta-analytic models. Between study heterogeneity was tested using the I^2 statistic (22). Due to lack of evidence of parameter heterogeneity, we present results from the fixed effects meta-analytic models.

RESULTS

Among the 201,492 women who completed the baseline questionnaire and were included in this analysis, 651 incident bladder cancer cases were diagnosed. Demographic factors were similar between the women who completed the 1995–1996 questionnaire and the women who completed the 1996–1997 questionnaire (Table I).

We observed a statistically significant inverse association with bladder cancer among parous compared to nulliparous women (HR=0.76; 95% CI 0.62–0.93) (Table II). No significant linear trend was observed with increasing number of live-born children (p_{trend}=0.05). Compared to nulliparous women, women who reported being ≤ 19 years of age at first birth had the greatest reduction in risk of bladder cancer, while no statistical difference in risk was seen among women who reported age at first birth at 25 or older (P_{trend}=0.67). No

significant differences in association among parous women were noted by smoking status ($P_{interaction}$=0.85).

A small, nonsignificant elevation in risk for bladder cancer was found for women who reported menopause at 45–49 years of age compared to women who reported menopause at 50–54 years of age, after multivariate adjustment (HR=1.22; 95% CI 0.98–1.50). Similar associations were observed in analyses restricted to natural menopause. Women who reported radiation or chemotherapy as the reason for their menopause experienced statistically significant elevation in risk of bladder cancer (HR=6.85; 95% CI 2.19–21.5) compared to women who reported natural menopause between 50–54 years of age.

When we stratified by smoking status, no association with early age at natural menopause and bladder cancer was observed among nonsmoking women (45–49 years HR=1.20; 95% CI 0.72–2.01). A statistically significant association was observed among former smokers for women reporting natural menopause at 45–49 years of age (HR=1.44; 95% CI 1.03–2.01), although no association was seen among current smokers (HR=0.98; 95% CI 0.63–1.52). Body mass index did not modify the associations with early age at menopause ($P_{interaction}$ ≥0.85) (data not shown).

We observed an inverse association with bladder cancer and later age at menarche (p_{trend}=0.03) with the greatest reduction in risk among women who reported menarche at age 15 or later compared to women who experienced menarche at 10 or younger (HR=0.57; 95% CI 0.39–0.84). No significant associations were observed for duration of oral contraceptive use or hysterectomy.

EPT

Among the 127,361 women who completed the 1996–1997 questionnaire and were followed through June 30, 2002, 198 incident bladder cancer cases were identified. Nearly 60% of all women in the NIH-AARP cohort reported ever having used MHT on the second questionnaire, with close to 30% reporting ever use of combined estrogen and progestin and nearly 30% reporting ever use of estrogen alone (Table I). Women who reported use of EPT were more likely to be younger, Caucasian, have a lower body mass index, and have a college degree while EPT users were less likely to report a hysterectomy, being a current smoker, or being postmenopausal compared to non-MHT users. Compared to non-MHT users, estrogen only users were more likely to report having had a hysterectomy, having a lower body mass index, and being postmenopausal, younger, and Caucasian.

A statistically significant inverse association was observed for women who reported only using combined estrogen and progestin therapy (HR=0.59; 95% CI 0.35–0.97) compared to women who reported no MHT use (Table III). Similar associations were seen with ever EPT users, once all women who had used EPT, regardless of formulation differences prior to or after EPT use, were combined (HR=0.53; 95% CI 0.34–0.83) (Table IV). An inverse association among former and current EPT users was observed, with only former users reaching statistical significance (HR=0.33; 95% CI 0.16–0.67). A 60% reduction in risk among women who reported using combined EPT for 10 years or less was observed, while no significant reduction in risk was seen among women who used for more than 10 years (HR=0.85; 95% CI (0.47–1.51; P_{trend}=0.15). When we combined recency and duration, the strongest inverse association was seen among EPT users of <10 years, regardless of recency (former, <10y: HR=0.30; 95% CI: 0.13–0.67; current, <10y: HR=0.49; 95% CI: 0.26–0.93), although the case numbers among long-term users were too small to draw any meaningful conclusions (former, ≥10y: HR=0.53; 95% CI: 0.13–2.20; current, ≥10y: HR= 0.91; 95% CI: 0.49–1.68). Women who followed a continuous EPT regimen had a 50 % reduction in risk (HR=0.52; 95% CI 0.31–0.89), while an inverse, but not statistically significant,

association was seen among women who reported sequential EPT regimen use (HR=0.61; 95% CI 0.34–1.10). When we restricted the analysis to urothelial cancers only, we observed a slightly stronger inverse association with EPT (HR= 0.48; 95% CI: 0.30–0.77).

All inverse associations for women who reported use of EPT and did not report having a hysterectomy on the baseline questionnaire were consistent or stronger than the overall estimates, despite smaller numbers. The association between EPT use and bladder cancer risk was very similar when we restricted the analysis to postmenopausal women only (HR=0.56; 95% CI 0.36–0.87). No significant interactions were observed with smoking status or body mass index (all $P_{interaction} > 0.78$) (data not shown).

In the sensitivity analyses that used the time-dependent MHT duration and recency variables, current EPT users had a significant risk reduction of greater than 50% (HR=0.48; 95% CI 0.23–0.98). The statistically significant inverse association with EPT use for less than 10 years remained, while the inverse association with longer term EPT use was stronger than the estimate in the main analysis, but the confidence interval included 1.00 (HR=0.52; 95% CI 0.22–1.22; $P_{trend}=0.14$). No significant heterogeneity between the two samples was observed for EPT only recency or duration (all $P_{heterogeneity}>0.08$).

A 40% reduction in risk for bladder cancer was observed among estrogen and progestin users in the fixed effects meta-analysis (HR=0.61; 95% CI 0.47–0.78). No significant heterogeneity was observed between the study-specific HRs overall ($P_{heterogeneity}=0.81$) (Figure I).

Unopposed estrogen

No significant associations with bladder cancer were identified among women who reported ever use of ET only (HR=0.82; 95%CI 0.58–1.15) or by recency of ET use ($p_{trend}=0.11$). No association was seen with short term use of ET; however, a significant inverse association was observed for long-term users of ET (HR=0.61; 95% CI 0.38–0.99; $P_{trend}=0.07$) (Table V). When we combined recency and duration, the inverse association remained among the long-term users, but was not significant (current ET only, ≥10y: HR= 0.69, 95% CI: 0.43–1.12).

Associations for recency and duration of estrogen only use among women who reported a hysterectomy on the baseline questionnaire were closer to the null or no longer statistically significant. The association between ET use and bladder cancer risk remained unchanged when we restricted the analysis to postmenopausal women only (HR=0.82; 95% CI 0.58–1.15). No significant interactions by smoking status or body mass index were identified for ET only use (all $P_{interaction} \geq 0.57$). When we restricted the analysis to urothelial cancers only, we observed no association with ET only use (HR= 0.85; 95% CI: 0.60–1.19).

No significant associations were observed when the time-varying covariates were used to update recency of ET only use (current ET use: HR=0.72; 95% CI (0.41–1.27) and ET only duration (ET use 10+ years: HR= 0.85; 95% CI (0.48–1.49), $P_{trend} = 0.49$). When we tested for differences in parameter estimates based solely on ET exposure reported on the 1996–1997 questionnaire among women who answered the 1996–1997 questionnaire compared to those who completed both the 1996–1997 and 2004 questionnaire, no heterogeneity between the two samples was observed for ET only ever use or recency (all $P_{heterogeneity}>0.72$); however, significant heterogeneity was observed between the two samples for ET duration and bladder cancer, suggesting the duration associations were not robust (all $P_{heterogeneity}>0.02$).

No association with bladder cancer risk and estrogen use alone was observed in the fixed effects meta-analysis (HR=1.03; 95% CI 0.87–1.24). No significant heterogeneity was observed between the study-specific HRs overall ($P_{heterogeneity}$=0.45) (Figure I).

DISCUSSION

We observed a reduced risk of bladder cancer among parous compared to nulliparous women and among women who reported later age at menarche. An elevated bladder cancer risk was observed among women who reported menopause at age 45–49 and among women who reported menopause as a result of radiation or chemotherapy. No associations were observed for duration of oral contraceptive use or hysterectomy status. We also observed an inverse association among women who reported EPT use compared to women who reported no MHT use, while little or no associations were observed among women who reported using estrogen therapy alone.

Parity has been shown to be inversely associated with bladder cancer risk (7), although not all studies reported significant results (9;10;13;14), and some studies only found the reduction in risk among non-smokers (7;23;24). Two recent meta-analyses reported a 30% reduction in risk overall among parous women with no heterogeneity among study estimates (7;8). Our findings support the inverse association between parity and bladder cancer. Most studies, including ours, did not find a trend in risk reduction with increasing number of live-births. This lack of trend suggests a threshold effect in which the protective mechanism related to parity is established after the first birth. While several studies have not found an association between bladder cancer and age at first birth (9;13;14;23;24), our findings, as well as others (7), suggest risk of bladder cancer may be lowest among women who experience their first pregnancy at an early age (≤19 years), indicating that the initiating events or mechanisms that protect against these events may occur early in life. Pregnancy is associated with dramatic changes in estrogen and progesterone levels; however, how these changes in sex steroid hormone levels directly influence risk for bladder cancer later in life remains unclear.

Early age at menopause has been associated with an elevated risk of bladder cancer in several cohort studies (9;14), although not all elevations were statistically significant (13) and several studies found no association (7;12;24). While we did find evidence of an increased risk among women who experienced natural menopause between the ages of 45–49, no association was found among the women who reported experiencing natural menopause at the earliest age (≤44years). Since the climacteric period may extend over several months or years, self-reported age at menopause has been shown to have moderate validity and reliability (25–28), depending on time since menopause (25;26;28), age (28), and reason for menopause, with women reporting age at surgical menopause with greater accuracy than women who experience natural menopause (25;26;28). One study found women who experience menopause early (<45 years of age) tend to overestimate their age at menopause (29). Misclassification of self-reported age at menopause could explain our lack of association with bladder cancer risk among the women who experienced natural menopause at the earliest age (≤44 years).

In addition to potential misclassification, residual confounding by smoking status should also be considered as a possible explanation for the association between early age at menopause and bladder cancer. Women who smoke experience an earlier age at menopause than women who do not smoke (30). Although the number of women reporting the earliest age at natural menopause was small in our study, no significant elevation in risk was seen for ≤ 44years of age or 45–49 years of age among nonsmokers, suggesting the elevation in risk observed may have been due to residual confounding.

The elevated bladder cancer risk that we found among women who reported radiation or chemotherapy as the reason for their menopause has not been reported previously. Although this finding may be due to chance given the small numbers, the bladder has been shown to be a radiation-sensitive organ since individuals exposed to radiation are at increased risk for a second primary bladder cancer (31;32). Moreover, cyclophosphamide, an alkylating agent used to treat some malignant diseases, has been shown to be associated with a dose-dependent increase in risk for bladder cancer among cancer survivors (1).

We observed more than a 40% reduction in risk for bladder cancer among women who reported menarche at 15 years of age or older compared to women who reported menarche at 10 years or younger. While several studies have observed no association (7;9;13;24), two studies did report an inverse association with later age compared to earlier age at menarche, although these associations were not statistically significant (10;14). While chance cannot be ruled out as an explanation, early exposure to sex hormones may influence events related to carcinogenesis as similar associations with age at menarche have been observed for lung cancer (33) and breast cancer (34).

Many epidemiological studies have either not found an association between bladder cancer and hormone therapy overall (9;10) or reported an elevated association (8;11;12); however, findings from three recent cohort studies have suggested that risk of bladder cancer may differ by formulation (7;13;14). All three studies found an inverse association with EPT use, although only one reported statistically significant results (7). Duration of EPT use, however, was not presented in either of these papers, probably because small numbers in these studies precluded a meaningful evaluation. Only one other study reported on duration of EPT use and no significant trend was observed (7). Our findings are consistent with these published studies. We found a 40–50% reduction in risk of bladder cancer among women who reported EPT use in our study and in the meta-analysis, with similar inverse associations seen among current EPT users in our study. We did not, however, observe an association with long term users of EPT (10+years). Even in the sensitivity analysis, with updated recency and duration exposure status, the inverse association was not statistically significant and no linear trend was identified. If EPT use played a significant role in the etiology of bladder cancer, we would expect to see the strongest inverse association among the long-term users. Lack of power due to small numbers or non-differential misclassification could account for the lack of association among long-term users. Self-reported ever use of MHT has been shown to be accurate and reliable, although the reliability decreases for more specific details related to duration, age at starting and stopping use, and dose (27;35–37). Chance is an unlikely explanation for our findings because of the consistent inverse association that has been observed between EPT use and bladder cancer across multiple cohorts. Lastly, a third unidentified confounding factor that is related to reasons for starting or stopping EPT use and also associated with bladder cancer risk could have contributed to our overall findings.

No association between bladder cancer risk and estrogen only therapy was observed in any of the three previous cohorts (7;13;14). Current use of ET was not associated with bladder cancer (13) (14) and neither was duration of ET use (P_{trend}=0.50), although only one previous study presented findings on duration of ET use (13). Our study results overall and the meta-analysis found no association between ET use only and bladder cancer risk. Although we observed an inverse association with long-term ET use, the association was not consistently replicated by hysterectomy status or in the time-varying model.

The exact mechanisms through which estrogen and progesterone operate to affect bladder cancer risk over the course of a lifetime remain unknown. While some experimental studies have shown estrogen can inhibit the development and growth of chemically-induced bladder

cancer(4;6), other studies have shown increased expression of estrogen receptor-β (ER-β) to be associated with more aggressive stage and grade (38). Moreover, selective estrogen receptor modulators, such as tamoxifen and raloxifene, have been shown to reduce proliferation of bladder cancer cell lines and reduce growth of bladder tumors in vivo (38;39). Whether progesterone plays an antiestrogenic role in the bladder is not known; however, its antagonistic effects on estrogen-induced cell proliferation have been described, particularly as it relates to the endometrium (40;41). Interestingly, PR expression levels have been shown to be higher among post-menopausal women who report use of MHT compared to post-menopausal women who do not use MHT (42).

Our study provided a detailed assessment of MHT including an evaluation of MHT by formulation, regimen, recency, and duration of use. The NIH-AARP study was implemented at a time when use of MHT was increasing in the United States, particularly among women over 60 years of age (43). Therefore, a large number of our participants reported exposure to MHT increasing our power to detect an association. We were able to minimize misclassification of MHT use over time by incorporating updates of recency and duration for a large subset of the study participants.

In conclusion, our findings confirm a reduction in risk for bladder cancer among parous women, women who reported later age at menarche and women who reported use of combined EPT therapy. Our findings add to the growing body of evidence that formulation type is an important consideration when evaluating risk for bladder cancer, underscoring the need for future pooling efforts to more extensively explore the MHT associations for etiological purposes. In addition, the associations with later age at menarche and ≤19 years of age at first birth among parous women suggest that early hormonal events may contribute to the initiation of tumor development. Our findings suggest that sex steroid hormones throughout a woman's lifetime may play an etiologic role in the risk of bladder cancer.

Acknowledgments

This research was supported by the Intramural Research Program of the NIH, National Cancer Institute, U.S. National Institutes of Health. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

NIH-AARP Diet and Health Study research was supported [in part] by the Intramural Research Program of the NIH, National Cancer Institute. Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System (FCDC) under contract with the Florida Department of Health (FDOH). The views expressed herein are solely those of the authors and do not necessarily reflect those of the FCDC or FDOH. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations or conclusions. Cancer incidence data from Arizona were collected by the Arizona Cancer Registry, Division of Public Health Services, Arizona Department of Health Services. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services.

We are indebted to the participants in the NIH-AARP Diet and Health Study for their outstanding cooperation. We also thank Sigurd Hermansen and Kerry Grace Morrissey from Westat for study outcomes ascertainment and management and Adam Rischat Information Management Services for data support and analysis.

Inmemoriam for Dr. Arthur Schatzkin, visionary investigator who founded the NIH-AARP Diet and Health Study.

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Novelty and impact

The association between bladder cancer risk among women and menopausal hormone therapy (MHT) may differ by formulation; however, few studies have evaluated this hypothesis. Our findings confirm and build on the growing body of evidence that formulation type is an important consideration when evaluating risk for bladder cancer, underscoring the need for future pooling efforts to more extensively explore the MHT associations for etiological purposes.

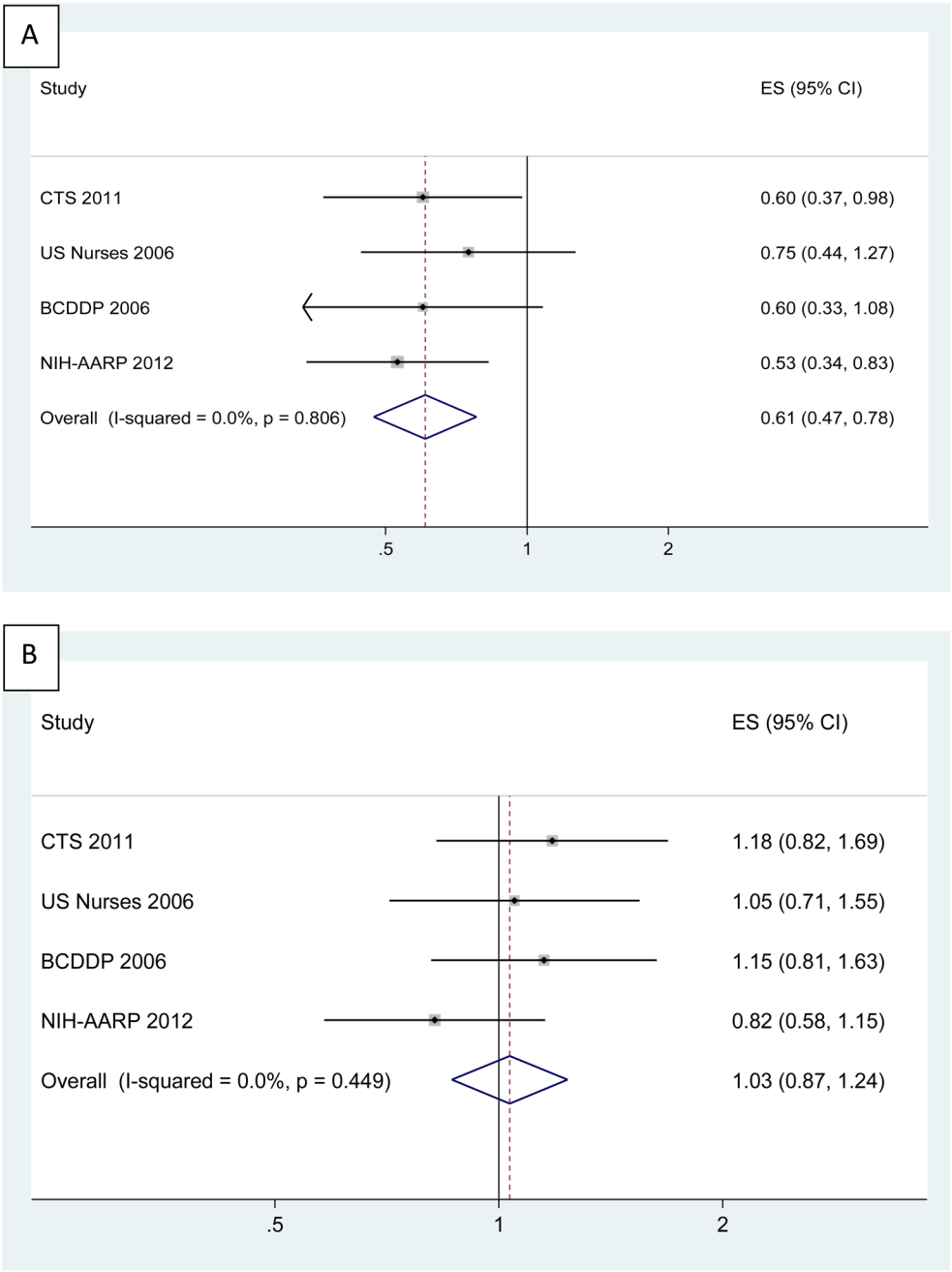

Figure I.

Forrest plots of meta-analysis results of association between menopausal hormone therapy and risk of bladder cancer A) estrogen and progestin B) estrogen only

Int J Cancer. Author manuscript; available in PMC 2014 July 15.

Table I

Demographic factors among women on the baseline questionnaire(1995–1996)and by ever use of menopausal hormone therapy on the second questionnaire(1996–1997), NIH-AARP Diet and Health Study

Variable	1995–1996	1996–1997			
	All	All	No MHT	Estrogen	EPT	Other/uk
Cohort (n) (%)	201,492	127,361	49657 (39.0)	35249 (27.7)	36492 (28.7)	5865 (4.6)
Case(n)	651	198	96	52	39	10
Age(%)						
<55 years	14.0	11.3	10.3	9.5	14.3	11.5
55–59 years	22.8	21.8	17.0	21.3	28.7	23.0
60–64 years	28.2	28.0	26.8	28.5	29.1	27.9
65–69 years	31.5	32.0	37.3	33.3	23.6	31.2
>=70 years	3.5	6.9	8.6	7.4	4.2	6.6
WhiteRace	89.4	90.8	88.8	91.3	93.6	88.4
BMI (kg/m^2)(%)						
18.5-<25.0	41.3	42.8	37.4	42.2	50.9	41.6
25 to<30.0	31.4	31.4	31.5	32.7	29.7	32.3
≥ 30.0	20.8	20.0	23.8	20.1	14.8	19.8
unclassifiable	3.3	3.1	3.9	2.5	2.4	3.2
missing	3.2	2.8	3.4	2.6	2.2	3.1
Education(%)						
11 yrs or less	6.3	5.3	6.9	5.4	2.6	7.2
12 years or high school	25.3	24.4	29.4	24.8	17.2	24.5
Techor some college	35.3	35.7	33.3	38.8	36.0	36.2
College or post graduate	29.7	31.8	27.5	27.8	42.0	28.5
missing	3.4	2.9	3.0	3.1	2.3	3.6
Smoke(%)						
Never	43.5	44.4	45.2	44.6	43.1	44.5
Former	38.7	39.2	36.2	39.3	43.0	39.5
Current	14.2	13.3	15.3	13.0	10.8	12.7
Missing	3.6	3.2	3.3	3.0	3.1	3.3

Variable	1995–1996	1996–1997				
	All	All	No MHT	Estrogen	EPT	Other/uk
Hysterectomy at baseline(%)	42.2	40.4	21.0	84.1	22.1	55.3
Postmenopausal(%)	93.5	93.5	94.0	98.1	88.6	93.6

Table II

Association between hormone and reproductive factors and bladder cancer riskon the baseline questionnaire (1995–1996), NIH-AARP Diet and Health Study, 1995–2006

Variable	Cases	Personyears	Hazard Ratio (95% CI)*		Hazard Ratio (95% CI)**	
Parity+						
No	110	264,009	1.00	Ref	1.00	Ref
Yes	527	1,578,883	0.75	0.61–0.92	0.76	0.62–0.93
						0.008
Number of children+						
No children	110	264,009	1.00	Ref	1.00	Ref
1	66	194,778	0.81	0.60–1.10	0.78	0.58–1.07
2	144	487,167	0.70	0.54–0.89	0.72	0.56–0.92
3–4	242	686,295	0.77	0.61–0.97	0.78	0.62–0.98
5+	75	210,644	0.72	0.54–0.97	0.73	0.54–0.98
$\mathbf{P_{trend}}$						0.05
Age at First Birth+						
No children	110	264,009	1.00	Ref	1.00	Ref
<=19	87	328,018	0.64	0.48–0.84	0.59	0.45–0.78
20–24	279	808,361	0.76	0.61–0.95	0.78	0.62–0.97
25–29	126	328,880	0.83	0.64–1.07	0.89	0.69–1.15
30+	33	107,881	0.66	0.45–0.98	0.72	0.49–1.06
$\mathbf{P_{trend+}}$						0.67
Age at Menopause++#						
<45	141	393,293	1.11	0.89–1.38	0.98	0.79–1.22
45–49	166	391,939	1.31	1.06–1.62	1.22	0.98–1.50
50–54	179	551,146	1.00	Ref	1.00	Ref
>=55	39	119,621	0.92	0.65–1.30	0.98	0.69–1.38
$\mathbf{P_{trend}}$						0.71
Reason for menopause++						
Natural						
<45	48	120,181	1.14	0.83–1.58	0.98	0.71–1.35

Variable	Cases	Personyears	Hazard Ratio (95% CI)*		Hazard Ratio (95% CI)**	
45–49	127	282,841	1.36	1.08–1.71	1.24	0.98–1.56
50–54	164	492,001	1.00	Ref	1.00	Ref
>=55	37	108,792	0.94	0.65–1.34	1.00	0.70–1.43
Surgery	147	450,066	0.99	0.79–1.24	0.95	0.76–1.18
Medical	3	1,106	8.40	2.68–26.3	6.85	2.19–21.5
Premenopausal	10	70,531	0.92	0.47–1.79	0.99	0.51–1.93
Unknown	19	61,997	0.94	0.59–1.51	0.93	0.57–1.51
Age at Menarche						
<=10	56	126,833	1.00	Ref	1.00	Ref
11–12	269	782,230	0.72	0.54–0.96	0.75	0.56–1.01
13–14	274	775,177	0.72	0.54–0.96	0.77	0.57–1.02
>=15	47	176,662	0.54	0.36–0.79	0.57	0.39–0.84
$\mathbf{P_{trend}}$						0.03
Oral Contraceptives						
No OC use	419	1,108,244	1.00	Ref	1.00	Ref
1–4	99	330,705	1.05	0.84–1.31	1.01	0.81–1.26
5–9	69	232,701	1.04	0.80–1.34	1.00	0.77–1.30
10+	56	179,945	1.05	0.79–1.39	1.02	0.77–1.36
$\mathbf{P_{trend}}$						0.91
Hysterectomy						
No	388	1,085,074	1.00	Ref	1.00	Ref
Yes	253	769,645	0.89	0.76–1.05	0.90	0.77–1.06

*age-adjusted

**adjusting for age, smoking status, number of cigerattes smoked per day, and body mass index

+14 cases were missing information on parity, 2 additional cases were missing information on age at first birth

++excluding 96cases and 31,396 individuals who reported a hysterectomy with intact ovaries due to unknown menopausal status.

#10 premenopausal case and 20 cases with unknown age at menopause not shown.

Table III

Association between bladder cancer risk and MHT formulation on the second questionnaire(1996–1997), NIH-AARP Diet and Health Study, 1996–2002

Variable	Cases*	Personyears	Hazard Ratio(95% CI)**		Hazard Ratio (95% CI)***	
Formulation Order+						
No MHT	96	258,677	1.00	(Ref)	1.00	(Ref)
ET	52	184,120	0.79	0.56–1.11	0.82	0.58–1.15
ET-EPT	4	27,675	0.40	0.15–1.09	0.42	0.16–1.15
EPT	19	117,212	0.55	0.33–0.90	0.59	0.35–0.97
UK-start for ET and/or PT	13	22,448	1.61	0.90–2.88	1.70	0.95–3.04
UK	10	30,523	0.95	0.50–1.82	0.97	0.50–1.86

*3 bladder cancer cases developed in women who reported other combinations of EPT, ET or unopposed progestin, 1 case was missing formulation data

**age-adjusted

***adjusting for age, smoking status, number of cigerattes smoked per day, and body mass index

+MHT=menopausal hormone therapy; ET=estrogen therapy; EPT=estrogen and progestin therapy; PT=progestin therapy; UK=unknown

Table IV

Associations between risk of bladder cancer and combined estrogen and progestin therapy (EPT) use reported on the second questionnaire(1996–1997) among women overall and without hysterectomy, NIH-AARP Diet and Health Study, 1996–2002

Variable[+]	Case	Personyears	Overall[*]		Case	Personyears	No hysterectomy[*]	
EPT use								
No	96	258,677	1.00	(Ref)	79	200,174	1.00	(Ref)
Yes	26	167,734	0.53	0.34–0.83	21	132,847	0.51	0.31–0.84
Recency of EPT use[**]								
No MHT	96	258,677	1.00	(Ref)	79	200,174	1.00	(Ref)
Former	5	56,132	0.33	0.16–0.67	2	26,102	0.35	0.14–0.85
Current	20	110,258	0.65	0.40–1.04	18	105,749	0.56	0.34–0.94
				0.04				0.02
Duration of EPT use								
No MHT	96	258,677	1.00	(Ref)	79	200,174	1.00	(Ref)
<10	15	127,986	0.41	0.24–0.69	12	99,831	0.43	0.24–0.76
10+	11	39,001	0.85	0.47–1.51	9	32,728	0.71	0.37–1.38
P_{trend}				0.15				0.09
EPT Regimen[**]								
No MHT	96	258,677	1.00	(Ref)	79	200,174	1.00	(Ref)
Sequential	11	62,663	0.61	0.34–1.10	8	48,391	0.62	0.32–1.19
Continuous	14	91,512	0.52	0.31–0.89	12	76,764	0.48	0.26–0.86

[+] EPT=estrogen and progestin therapy ; MHT=menopausal hormone therapy

[*] adjusting for age, smoking status, number of cigerattes smoked per day, and body mass index

[**] 1 case is missing data on EPT recency and regimen

Table V

Associations between risk of bladder cancer and estrogen only use reported on the second questionnaire(1996–1997)among women overall and with hysterectomy, NIH-AARP Diet and Health Study, 1996–2002*

Variable+	Case	Personyears	Overall		Case	Personyears	Hysterectomy	
Ever ET								
No	96	258,677	1.00	(Ref)	16	54,727	1.00	(Ref)
Yes	52	184,120	0.82	0.58–1.15	41	155,059	0.98	0.55–1.76
Recency of ET use								
No MHT	96	258,677	1.00	(Ref)	16	54,727	1.00	(Ref)
Former	23	50,742	1.14	0.72–1.80	14	32,686	1.45	0.71–2.98
Current	29	131,289	0.68	0.45–1.03	27	121,002	0.84	0.45–1.58
				0.11				0.47
Duration of ET use								
No MHT	96	258,677	1.00	(Ref)	16	54,727	1.00	(Ref)
<10	32	91,391	1.07	0.71–1.60	22	67,131	1.38	0.72–2.66
10+	20	90,776	0.61	0.38–0.99	19	86,519	0.75	0.38–1.46
P_{trend}				0.07				0.45

*adjusting for age, smoking status, number of cigarettes smoked per day, and body mass index

+ET=estrogen therapy; MHT=menopausal hormone therapy