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Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

A Pooled Analysis of Reproductive Factors, Exogenous Hormone Use, and Risk of Multiple Myeloma among Women in the International Multiple Myeloma Consortium

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Abstract

Background: Female sex hormones are known to have immunomodulatory effects. Therefore, reproductive factors and exogenous hormone use could influence the risk of multiple myeloma in women. However, the role of hormonal factors in multiple myeloma etiology remains unclear because previous investigations were underpowered to detect modest associations.

Methods: We conducted a pooled analysis of seven case–control studies included in the International Multiple Myeloma Consortium, with individual data on reproductive factors and exogenous hormone use from 1,072 female cases and 3,541 female controls. Study-specific odds ratios and corresponding 95% confidence intervals (CI) were estimated using logistic regression and pooled analyses were conducted using random effects meta-analyses.

Results: Multiple myeloma was not associated with reproductive factors, including ever parous [OR = 0.92; 95% confidence interval (CI), 0.68–1.25], or with hormonal contraception use (OR = 1.04; 95% CI, 0.80–1.36). Postmenopausal hormone therapy users had nonsignificantly reduced risks of multiple myeloma compared with never users, but this association differed across centers (OR = 0.65; 95% CI, 0.37–1.15, I^2 = 76.0%, $P_{\text{heterogeneity}}$ = 0.01).

Conclusions: These data do not support a role for reproductive factors or exogenous hormones in myelomagenesis.

Impact: Incidence rates of multiple myeloma are higher in men than in women, and sex hormones could influence this pattern. Associations with reproductive factors and exogenous hormone use were inconclusive despite our large sample size, suggesting that female sex hormones may not play a significant role in multiple myeloma etiology. *Cancer Epidemiol Biomarkers Prev; 25(1); 1–5. ©2015 AACR.*

Introduction

Multiple myeloma is a malignancy characterized by the accumulation of clonal plasma cells in the bone marrow, abnormal secretion of monoclonal protein, and end organ damage (1). Incidence rates are higher in men than in women (2). Because female sex hormones have immunomodulatory effects, reproductive factors, and exogenous hormone use may affect risk for

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Table 1. Associations between reproductive factors and exogenous hormone use and multiple myeloma risk

	Co	Ca	Pooled OR (95% CI)*	*I2*	$P_{heterogeneity}$
Reproductive factors					
Age at menarche[a]					
Total	1,335	482			No. centers = 4
≤11	256	86	Ref		
12–13	717	271	1.20 (0.89–1.63)	0.0%	0.58
≥14	362	125	1.03 (0.73–1.45)	0.0%	0.57
Ever pregnant[c]					
Total	2,321	691			No. centers = 6
No	228	69	Ref		
Yes	2,093	622	0.90 (0.57–1.44)	48.2%	0.09
No of pregnancies[b]					
Total	1,494	593			No. centers = 5
None	142	64	Ref		
1	145	52	0.80 (0.39–1.64)	55.2%	0.06
2	329	134	0.83 (0.57–1.20)	0.0%	0.78
3	296	118	0.90 (0.50–1.60)	51.8%	0.08
≥4	582	225	0.91 (0.54–1.54)	50.3%	0.09
Ever parous[d]					
Total	3,075	1,007			No. centers = 7
Never	408	150	Ref		
Ever	2,667	857	0.92 (0.68–1.25)	41.8%	0.11
No of children[d]					
Total	3,075	1,007			No. centers = 7
None	408	150	Ref		
1	410	138	0.95 (0.66–1.38)	30.9%	0.19
2	802	274	0.96 (0.75–1.24)	0.0%	0.46
3	635	190	0.91 (0.60–1.37)	53.1%	0.05
≥4	820	255	0.91 (0.64–1.30)	41.3%	0.12
Age at first birth[e]					
Total	1,941	449			No. centers = 4
Nulliparous	255	64	Ref		
<20	237	66	0.97 (0.50–1.89)	54.4%	0.09
20–<25	749	167	0.99 (0.58–1.70)	56.1%	0.08
25+	700	152	0.96 (0.59–1.57)	44.8%	0.14
Age at menopause[b]					
Total	1,265	524			No. centers = 5
≤45	414	184	Ref		
45–49	313	118	1.00 (0.74–1.35)	0.0%	0.46
≥50	538	222	1.12 (0.86–1.45)	0.0%	0.58
Cause of menopause[f]					
Total	800	397			No. centers = 4
Natural	433	197	Ref		
Surgical/therapeutic	367	200	1.11 (0.80–1.54)	36.7%	0.19
Exogenous hormone use					
Ever hormonal contraception[g]					
Total	2,450	590			No. centers = 5
Never used	1,805	426	Ref		
Ever used	645	164	1.04 (0.80–1.36)	0.0%	0.66
Age at first hormonal contraception[g]					
Total	2,434	587			No. centers = 5
Never used	1,805	426	Ref		
≤25	421	101	1.07 (0.76–1.49)	0.0%	0.80
>25	208	60	1.08 (0.76–1.54)	0.0%	0.42
Year at first hormonal contraception[g]					
Total	2,434	587			No. centers = 5
Never used	1,805	426	Ref		
<1975	353	119	1.19 (0.87–1.62)	0.0%	0.87
≥1975	276	42	1.18 (0.65–2.14)	19.6%	0.29
Time since last hormonal contraception[g]					
Total	2,421	588			No. centers = 5
Never used	1,891	428	Ref		
≤20	275	70	1.22 (0.84–1.76)	0.0%	0.50
>20	255	90	1.09 (0.75–1.58)	15.2%	0.32
Years of hormonal contraception[g]					
Total	2,415	582			No. centers = 5
Never used	1,805	426	Ref		
<5	217	69	1.30 (0.92–1.83)	0.0%	0.89
≥5	393	87	0.96 (0.57–1.63)	55.6%	0.06

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Table 1. Associations between reproductive factors and exogenous hormone use and multiple myeloma risk (Cont'd)

	Co	Ca	Pooled OR (95% CI)*	*I2*	$P_{heterogeneity}$
Ever postmenopausal hormonal therapy[a]					
Total	1,076	432			No. centers = 4
Never used	703	307	Ref		
Ever used	373	125	0.65 (0.37–1.15)	76.0%	0.01
Age first used postmenopausal hormonal therapy[a]					
Total	1,057	425			No. centers = 4
Never used	703	307	Ref		
<50	197	72	0.60 (0.31–1.17)	71.5%	0.01
≥50	157	46	0.61 (0.41–0.90)	4.5%	0.37
Year first used postmenopausal hormonal therapy[a]					
Total	1,057	425			No. centers = 4
Never used	703	307	Ref		
<1980	143	54	0.58 (0.33–1.04)	38.9%	0.18
≥1980	211	64	0.81 (0.37–1.77)	75.3%	0.01
Time since last postmenopausal hormonal therapy consumption[a]					
Total	1,055	424			No. centers = 4
Never used	703	307	Ref		
Current	150	41	0.84 (0.30–2.38)	77.1%	<0.01
≤10	116	46	0.90 (0.37–2.16)	76.5%	0.01
>10	86	30	0.52 (0.21–1.26)	57.9%	0.07
Years of hormonal therapy use[a]					
Total	1,056	423			No. centers = 4
Never used	703	307	Ref		
<5	136	54	0.64 (0.30–1.37)	71.4%	0.01
≥5	217	62	0.56 (0.33–0.97)	57.6%	0.07

Abbreviations: Co, controls; Ca, cases.

*Adjusted for center, age (four categories), and race (white, black, and others).

[a]Studies with data on periods starting, ever postmenopausal hormonal therapy use, number of years postmenopausal hormonal therapy was used, years since last postmenopausal hormonal therapy consumption, and age at first post-menopausal HT use were LAMMCC, RPCI, NCI-Yale, and iMAGE. Analyses on postmenopausal hormonal therapy variables were performed among postmenopausal women.

[b]Analyses on periods stopping were performed among postmenopausal women. Analyses on number of pregnancies were performed among women aged 45 or older at reference date. Studies with data on periods stopping and number of pregnancies were LAMMCC, RPCI, NCI-Yale, iMAGE, and Utah.

[c]Among women ages 45 or older at reference date. Studies with data on ever being pregnant were LAMMCC, RPCI, NCI-Yale, iMAGE, Utah, and Epilymph.

[d]Among women ages 45 or older at reference date. All studies collected data on parity and number of children.

[e]Among women ages 45 or older at reference date. Studies with data on age at first child were RPCI, Epilymph, NCI-Yale, and iMAGE.

[f]Among postmenopausal women. Studies with data on cause of menopause were LAMMCC, RPCI, Utah, and iMAGE.

[g]Studies with data on hormonal contraception use, number of years hormonal contraception was used, years since last hormonal contraception consumption, and age at first hormonal contraception use were LAMMCC, RPCI, Epilymph, NCI-Yale, and iMAGE.

multiple myeloma. However, the role of hormonal factors in multiple myeloma etiology remains unclear. A few studies addressed possible associations between multiple myeloma risk and reproductive factors, such as parity (3–6) or use of postmenopausal hormone therapy (HT; refs. 6–8), but yielded inconsistent results as most studies were underpowered. We conducted a pooled analysis of case–control studies included in the International Multiple Myeloma Consortium (IMMC) to clarify the role of hormonal factors in the etiology of multiple myeloma.

Materials and Methods

We pooled individual-level questionnaire data from the seven IMMC case–control studies that collected information on reproductive factors among women (1,072 cases and 3,541 controls). These studies were: Los Angeles County Multiple Myeloma Case-Control Study (LAMMCC), Roswell Park Cancer Institute (RPCI), Utah, Epilymph, Fred Hutchinson Cancer Research Center (FHCRC) 1980s, National Cancer Institute (NCI)-Yale, and Molecular and Genetic Epidemiology Study (iMAGE). Enrollment period, age eligibility, study design, sample sizes, and participation rates within each study are summarized in Supplementary Table S1. Parity was defined as number of live births in NCI-Yale, iMAGE, and RCPI, and as number of children in all other studies.

Within each study, we computed ORs with corresponding 95% confidence intervals (CI) using unconditional logistic regression, adjusting for age group (four categories), race (except for Epilymph, which did not collect these data), and study center (for multicentric studies: Epilymph and FHCRC 1980s). Random-effects models were used to calculate pooled estimates using the DerSimonian and Laird method. Heterogeneity between studies was assessed using the I^2 statistic and $P_{heterogeneity}$ using the Mantel–Haenszel method. Analyses on parity and gravidity were restricted to women ages 45 or older, as they are likely to have completed their reproductive history. Analyses on hormonal therapy were restricted to postmenopausal women, defined as women who reported cessation of their menstrual periods. Wald tests were utilized to assess heterogeneity between strata.

Results

In this pooled analysis, we did not observe any statistically significant association between multiple myeloma and age at menarche or at menopause, ever pregnant, number of pregnancies, ever parous, number of children, age at first birth, or cause of menopause (Table 1). The association between multiple myeloma and ever use of hormonal contraceptives was not significant [OR = 1.04; 95% confidence interval (CI), 0.80–1.36; Table 1]. Similarly, we saw no significant associations or consistent patterns

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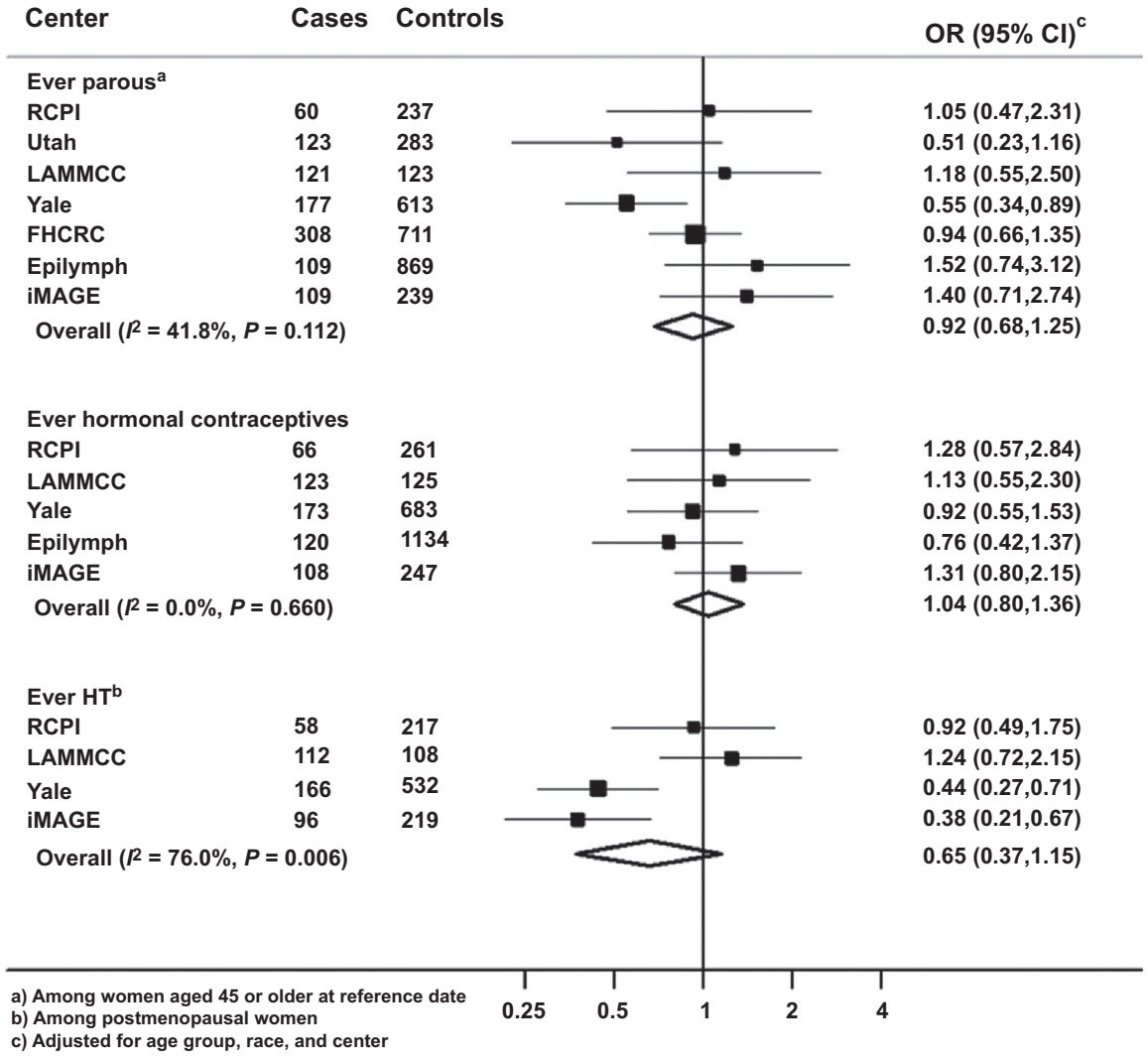

Figure 1.
Study-specific risks of multiple myeloma for ever versus never parous, hormonal contraceptives, and postmenopausal hormone therapy.

for age and year at first use, duration, or time since last hormonal contraceptive use.

Hormonal therapy use showed nonsignificant decreased risks of multiple myeloma (OR = 0.65; 95% CI, 0.37–1.15), but also showed significant heterogeneity between centers (I^2 = 76.0%; P = 0.01, Fig. 1). Further adjustment for BMI, education, tobacco, and alcohol yielded a similar risk estimate (OR = 0.70; 95% CI, 0.39–1.25). Inverse associations were observed among women taking hormonal therapy at ages 50 or older, or for more than 5 years, compared with never use (OR = 0.61; 95% CI, 0.41–0.90; and OR = 0.56; 95% CI, 0.33–0.97, respectively), although heterogeneity between centers hampered interpretation (Supplementary Fig. S1). Stratified analyses by cause of menopause, education, and BMI did not reveal statistically significant heterogeneity (data not shown).

Discussion

This large pooled analysis of 1,072 female cases and 3,541 controls yielded null associations between multiple myeloma and reproductive factors. To our knowledge, 3 case–control studies (3–5, 8) and 3 cohorts (4, 6, 7) have previously evaluated associations between reproductive factors, or exogenous hormone use and risk of multiple myeloma. Inconsistent results were observed for parity and multiple myeloma, with both significant inverse associations (5), increased risks (4), and null results (3, 6). Previously reported associations for hormonal

contraceptives and multiple myeloma have been null (5, 6). Significant inverse associations for hormonal therapy use were observed in an Italian case–control study (8), but these associations were not corroborated in two cohort studies (6, 7). However, conclusions in these studies have been limited by small sample sizes of women using hormonal therapy.

Our study was based on a large dataset with individual-level information on reproductive factors and exogenous hormone use, yet we did not observe consistent patterns with these factors and multiple myeloma risk. We had the ability to control for a variety of potential confounders, including education, BMI, and alcohol use. Ignoring these variables may have biased previous studies of hormonal therapy and cancer, due to the potential for selection bias and a healthy user effect. We did not observe clear evidence of confounding by those variables in the present analysis, although residual confounding cannot be discarded in explaining some of our results, in particular for hormonal therapy. Also, use of controls that may not be representative of the population from which the cases arose was an inherent limitation of some of the participating studies' design. In summary, our data do not support a significant role for reproductive factors or exogenous hormones in myelomagenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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