Maturitas 81 (2015) 323–326

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Misrepresentation of the risk of ovarian cancer among women using menopausal hormones. Spurious findings in a meta-analysis

Samuel Shapiro[a,*], John C. Stevenson[b], Alfred O. Mueck[c,d], Rod Baber[e]

[a] Epidemiology, Department of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
[b] National Heart and Lung Institute, Imperial College London, Royal Brompton Hospital, London, UK
[c] University Women's Hospital of Tuebingen, Tuebingen, Germany
[d] Beijing OB/GYN Hospital, Capital Medical University, Beijing, China
[e] Sydney Medical School, The University of Sydney, Sydney, NSW, Australia

ARTICLE INFO

Article history:
Received 20 March 2015
Accepted 24 March 2015

Keywords:
Menopausal hormone therapy
Risk of ovarian cancer
Validity

ABSTRACT

Background: Based on a meta-analysis of 52 studies, and principally on a meta-analysis of 17 follow-up studies, it has been claimed that current-or-recent use (last use <5 years previously) of menopausal hormones causes ovarian cancer, even if the duration of use was <5 years, and that women aged about 50 years who use hormones for >5 years have about one extra case per 1000 users, and one extra fatal case per 1700 users.
Objective: To evaluate the validity of the evidence.
Methods: Generally accepted epidemiological principles of causation were applied to the evidence.
Findings: The study base included hysterectomised women, an unknown proportion of whom were oophorectomised, and not at risk for ovarian cancer. The findings did not satisfy the criteria of time order, bias, confounding, strength of association, dose–response, duration–response, consistency, and biological plausibility.
Conclusions: The meta-analysis did not establish that current-or-recent use of menopausal hormones causes ovarian cancer. The strong likelihood is that early symptoms of as yet undiagnosed ovarian cancer "caused" current-or-recent short-duration hormone use, not the reverse. The representation of the number of extra cases, and fatal cases, among hormone users was misleading and alarmist.

1. Introduction

Beral and her colleagues, writing on behalf of the Collaborative Group on Epidemiological Studies of Ovarian Cancer, have recently reported on the risk of ovarian cancer among users of menopausal hormone therapy (MHT) in a meta-analysis of 52 studies [1,2]. The principal analyses, however, were confined to 17 follow-up studies. The risks for ever-use of MHT, for current or recent use (stopped <5 years before diagnosis), and for durations of current-or-recent use of <5 years and ≥5 years were significantly increased. Risks for current-or-recent use were increased for serous and endometrioid tumours, but not for mucinous or clear cell tumours.

The investigators concluded that "the increased risk may well be largely or wholly causal".

Below we evaluate the validity of the evidence.

2. Summary of the findings

In the 52 studies there were 21 488 cases, and in the 17 follow-up studies there were 6601 cases; the respective numbers of cases exposed to MHT were 9303 (43.3%) and 6601 (54.5%). To minimize the likelihood of bias, the principal analyses were confined to the follow-up studies. In sensitivity analyses, however, the combined data in all 52 studies were evaluated.

In the follow-up studies up to four randomly selected controls were matched to each case, and individual data were analysed as case-control comparisons. In a Danish study [3], because of data protection laws, individual data were not available; instead, tabulated data were provided by the Danish investigators, and incorporated into the analyses.

With never-use of MHT as the reference category, relative risk (RR) estimates were as follows: ever-use, 1.20 (99% confidence interval (CI) 1.13–1.28); current-or-recent use for durations of <5 years and >5 years, 1.43 (95% CI 1.31–1.56) and 1.37 (95% CI 1.29–1.43), respectively. Among women who used MHT for >5 years the risk declined after stopping, but was still elevated 10 years later

* Corresponding author. Tel.: +27 21 406 6459.
E-mail address: Samshap@mweb.co.za (S. Shapiro).

http://dx.doi.org/10.1016/j.maturitas.2015.03.018
0378-5122/

(RR 1.10; 95% CI 1.01–1.20). Among current-or-recent MHT users the RRs for serous and endometrioid tumours were 1.53 (95% CI 1.40–1.66) and 1.42 (95% CI 1.42 (95% CI 1.20–1.67), respectively; for mucinous and clear cell tumours the RRs were 0.93 and 0.75. A test for heterogeneity among the four histological subtypes was significant ($p < 0.0001$).

Under causal assumptions, the investigators estimated that "women who use [MHT] for 5 years around age 50 years have about one extra case per 1000 users and . . . about one extra ovarian cancer death per 1700 users".

3. Evaluation

Below, we apply generally accepted epidemiological criteria of causation [4,5] to the evidence from the meta-analysis. The criteria are inter-related, and when appropriate, we cross-refer. Before doing so, however, since the principal analyses were confined to the 17 follow-up studies, it is first necessary to mention that 49.7% (6022/12 110) of the cases were derived from the Million Women Study (MWS) [6] (our calculation; appendix [2] p. 10). One study only provided data for 1258 fatal cases [7]; among the remaining 16 studies the MWS cases accounted for 55.5% (6022/10 852) of all cases. Thus the overall findings in the follow-up studies were mainly driven by a single study, the MWS.

4. Time order

The strong likelihood is that as yet undiagnosed ovarian cancer "caused" current-or-recent MHT use for <5 years, not the reverse, and time order was violated. That violation was by far the most credible explanation, if not the entire explanation, of the increased risk of ovarian cancer associated with short-duration use. Common presenting symptoms of ovarian cancer include discomfort or pain during sexual intercourse, lower abdominal discomfort or pain, abdominal distension, urinary difficulties, and recurrent bladder infections. Each of these symptoms could selectively have resulted in the use of MHT before a diagnosis of ovarian cancer was made, because they were initially attributed to the menopause.

With the exception of the mortality study [7], it is likely that time order was violated in all the remaining 16 studies.

There is no experimental evidence to indicate that short-duration MHT induces ovarian carcinogenesis (see Section 12), further supporting the likelihood of violation of time order.

5. Specification of the study base

In the follow-up studies, among current-or-recent MHT users information on hysterectomy status was provided for only 34.3% (737/2151) of the exposed cases (our calculation; appendix p. 15). Among the 737 exposed cases, 550 (74.6%) had undergone hysterectomy.

Hysterectomised women who had their ovaries removed at the same time would commonly have been unaware of it, and the proportion of women in the study base who were not at risk for ovarian cancer was unknown. The investigators speculated that the inclusion of oophorectomised women would have resulted in underestimation of the RR [1,8]. That speculation is not defensible. Hysterectomised women who retained one or both ovaries, and who developed symptoms of as yet undiagnosed ovarian cancer, would selectively have been current-or-recent users of MHT (see Section 4). Among hysterectomised women who retained their ovaries it is also likely that on prolonged follow-up ovarian cancer would have been diagnosed earlier among MHT users than among non-users (see Section 6).

In the absence of information on hysterectomy status for 73.3% of current-or-recent users of MHT, coupled with likelihood that the majority had undergone hysterectomy, the findings in the meta-analysis were uninterpretable (see Section 7).

6. Bias

Among 2671 current-or-recent MHT-using cases 277 (10.4%) were borderline (our calculation; appendix p. 19).

Borderline tumours would selectively have been diagnosed among MHT users, because they would have undergone vaginal examinations more frequently than non-users, when they renewed their prescriptions. That bias would have occurred for all durations of use, and it would have occurred in all but the single mortality study [7]. For the same reason, malignant tumours would have been diagnosed earlier among MHT users than among non-users.

Follow-up rates among the 17 studies were not mentioned in the report or in the appendix. However, in a previous report from the MWS [6], the rate was 64%, and with the possible exception of the Danish study [3] it is likely that substantial proportions of MHT users were lost to follow-up. Users who developed ovarian cancer would less commonly have been lost to follow-up than users who did not (see the following section).

7. Confounding

As mentioned above, losses to follow-up were substantial, and women who developed symptoms of as yet undiagnosed ovarian cancer would selectively have been prescribed MHT (see Section 4), and selectively have been followed (see Section 6). Women who used MHT for >5 years would selectively have been followed after they stopped.

Also as mentioned above, among current-or-recent MHT users information on hysterectomy status was provided for only 34.3% of the cases (see Section 5), among whom 74.6% had undergone hysterectomy. Among the remaining cases with unknown hysterectomy status it is likely that a substantial proportion also had hysterectomies. With missing data for 65.7% of the cases, adjustment for confounding by hysterectomy status was not possible.

The investigators argued that the heterogeneity in the RRs for the four histological subtypes of ovarian cancer "argues strongly for causality, because it implies that the [MHT]-associated risks were not due just to confounding and that different ovarian cancer types have different causes."

That implication is not defensible [8,9]. First, it is not established that different subtypes of ovarian cancer have different causes. Second, histology can vary at different sites in the same tumour [9,10]. Third, among pathologists there is major discordance in diagnosing histological subtypes [9]. Fourth, in different studies different classifications of ovarian malignancies have been used [11]. For these reasons, precise and replicable diagnoses can only be made by pathologists with special training and experience in gynaecological pathology [9,11]. These considerations would have applied with added force to the meta-analysis, in which the quality of the pathological evidence across the studies would have varied.

In the absence of central and "blinded" audit, the histological classification presented in the meta-analysis was uninterpretable. And if, for the moment, that uninterpretability is set aside, since estrogen therapy causes endometrial cancer, a diagnosis of endometrioid ovarian cancer could selectively have been made by pathologists made aware of MHT use (see Section 6).