Comment on study by Backman et al. (2005)

BfArM acknowledges the submission of the manuscript by Backman et al. (2005) concerning the occurrence of breast cancer associated with Mirena® use. The manuscript was scheduled for publication in October 2005 and meanwhile has been published (Backman T. et al. Use of the Levonorgestrel-releasing intrauterine system and breast cancer. Obstet and Gynecol 2005;106:813-7). Unfortunately, the study has several flaws as detailed below and, hence, cannot be considered reassuring.

Summary of the publication
The objective of the study was to analyze the relationship between breast cancer and use of the LNG-IUD (Mirena®). The study was based on data from a large post-marketing study on Mirena® users (n=17,360) carried out in Finland. The results present an incidence comparison between Mirena® user data and the data on average Finnish female population (derived from the Finnish Cancer Registry), between 30 and 54 years of age. Based on 95% CI for the incidences of breast cancer, and Fischer’s exact test, the authors found no indication of a difference between the Mirena® users and the average Finnish female population in any of the 5-year age groups. The incidence rates per 100,000 WY are depicted in table 2). The authors conclude that the results suggest that the use of Mirena® is not associated with an increased risk of breast cancer. The study was funded by Schering OY, Turk Finland.

<table>
<thead>
<tr>
<th>LNG-IUD</th>
<th>average Finnish population</th>
<th>p-values (Fisher’s exact test)</th>
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</thead>
<tbody>
<tr>
<td>30-34</td>
<td>27.2</td>
<td>25.5</td>
</tr>
<tr>
<td>35-39</td>
<td><strong>74.0</strong></td>
<td>49.2</td>
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<tr>
<td>40-44</td>
<td>120.3</td>
<td>122.4</td>
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<tr>
<td>45-49</td>
<td>203.6</td>
<td>232.5</td>
</tr>
<tr>
<td>50-54</td>
<td>258.5</td>
<td>272.6</td>
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</tbody>
</table>

From the data presented (Fig. 1 of the publication) it can be learned that the age groups 35-39 and 40-44 account for 27% and 25% of the total exposure with Mirena®, respectively. The corresponding numbers of breast cancer cases were 30 (17%) and 46 (27%), respectively. The highest absolute number of breast cancer cases was observed in the age group 50-54 (n=54; 31%).

In the two age groups (30-34 and 35-39) the breast cancer incidences per 100,000 WY were higher for Mirena® users than in the average Finnish population (see table 2). It is noted that the difference in the age group 35-39 nearly missed statistical significance (p=0.056).

The authors also provide an analysis of breast cancer incidence among Mirena® users as a function of time elapsed from Mirena® insertion to the occurrence of breast cancer and did not find an apparent association. The authors conclude that this finding does not support a causal relationship between the use of Mirena® and the occurrence of breast cancer. However, a causal relationship cannot be totally excluded either.
As a summarizing conclusion the authors state in the discussion that „the post-marketing study does not support an association between Mirena® use and the development of breast cancer. On the other hand, an elevated breast cancer risk cannot be totally eliminated either, due to the limited control of confounding factors in the present study. Additional larger studies with a different methodological approach are needed to either confirm or refute the findings in this study.“

BfArM comments

The comments of the BfArM refer in particular to the methodology of the study. In general, the approach using a national cancer registry is feasible. However, no conclusions can be drawn from the study due to severe shortcomings.

1) There is no information about the characteristics of the women in the “comparator group”, e.g. risk factors including previous use of other hormonal contraceptives. Hence, no realistic comparison can be made.

2) It would be helpful to know on which basis the calculation of women-years for Mirena® users was made and how many women in each age group account for the number of women years stated. This could be interesting if the actual number of Mirena® users in the age group is low, despite the high number of women years, since the breast cancer incidence in the Finnish female population is based on a large number of women.

In fact, the high number of women years with Mirena® (cumulatively 151,844 according to fig. 1 of the manuscript) divided by the number of Mirena® users stated (n=17,360) would translate to an average use of the Mirena® of 8,7 years. Although some users could have had multiple subsequent insertions, this figure has to be confronted with a foreseen maximum use of 5 years according to the SPC and continuation rates of 93, 87, 81, 75, and 65% after 1, 2, 3, 4, and 5 years, respectively, as published by the same author (Backman 2000). Hence, the number of breast cancers among Mirena® users could refer to a smaller number of women years and, hence, the calculated breast cancer incidence could be higher in the Mirena® group.

Besides the comments on the methodology of the study the MAH is requested to comment on a striking result which is not addressed by the authors in the manuscript.

It is noted that the breast cancer incidence rate for Mirena® users per 100,000 WY in the age groups 30-34 and 35-39 was higher than for the overall Finnish female population. In particular, for Mirena® users aged 35-39 the breast cancer incidence rate per 100,000 WY was 74 whereas it was 49,2 for the overall Finnish female population (average). The p value was 0,056.

In the „higher“ age groups 40-44, 45-49, and 50-44 the breast cancer incidence rates per 100,000 WY for Mirena® users and the overall Finnish female population (average) are i) closer to each other (see fig. 2) and ii) the incidences were lower for the Mirena® group. This data constellation raises the question whether use of Mirena® could promote the growth of hormone-sensitive breast cancers which would lead to an earlier presentation of the disease and, hence, would reflect an increase in the number of breast cancer diagnoses, respectively the incidence, in the younger age group (35-39).
Information and comments requested from MAH

The BfArM asks the MAH

1) Please comment on the finding that the breast cancer incidence rate for Mirena® users per 100,000 WY in the age groups 30-34 and 35-39 was higher than for the overall Finnish female population. In particular, for Mirena® users aged 35-39 the breast cancer incidence rate per 100,000 WY was 74 whereas it was 49.2 for the overall Finnish female population (p value: 0.056).

2) Please provide further information which could help to overcome the shortcomings of the study. In particular, characterisation of the comparator group with regard to risk factors (including use of other hormonal contraceptives) is requested. In addition, please explain on which basis the calculation of women-years for Mirena® users was made and how many women in each age group account for the number of women years stated.

3) Please comment on the flaws of the study as outlined above.

Literature


