Oral contraceptive use and the risk of meningioma

Abstract:

Oral contraceptive use is a suspected risk factor for the development of a meningioma. This is supported by meningiomas being more common in females than males, the growth of meningiomas being affected by the menstrual cycle and the presence of estrogen, progestogen and androgen receptors on meningiomas. Some previous studies indicate an association between current use of oral contraceptives and the development of a meningioma, but most studies do not show an effect and are of low power to show an association. This case-control study aims to find out if there is an association between current or ever use of an oral contraceptive and developing a meningioma in pre-menopausal females. It also aims to look if this risk differs with hormone type. It does so by comparing cases in the three states of Eastern Australia of women aged between 16 and 45 who require surgical resection or biopsy of their meningioma with population-based controls.

Aims:

1. To prove that the use of an oral contraceptive pill is a risk factor for developing a meningioma in pre-menopausal women in Australia.
2. To determine whether the risk of a meningioma that is associated with taking oral contraceptives differs by current use, ever use and type of oral contraceptive.

Background:

Current oral contraceptive use is suspected to increase the risk of meningioma, but more studies need to be done in order to confirm this

association. (1) The most recent study found no increase in risk with ever use of oral contraceptives, but found an increased risk in current users of an oral contraceptive with an OR 1. 8, 95% CI 1. 1–2. 9 in pre-menopausal women. (1) This result is statistically significant at the 5% level.

The study was a case-control study which is appropriate as the outcome is rare and the exposure is common. The results from this study are limited from the fact that they only had 87 cases for pre-menopausal women who were using oral contraceptives, but since such a small sample size did pick up an association it makes it more likely to be a true association. This study had a wide variety of exposures they were looking for and so the statistically significant results that they did publish may have been due to chance from looking at so many possibilities. In regards to selection bias in this study the controls were selected by random digit dialling so this would have resulted in people who do not have access to a telephone from being excluded from the study. Controls did end up being more likely to be white, have 16 or more years of schooling and a salary greater than $75, 000. If people with these characteristics are more likely to be taking oral contraceptives then it would have resulted in an underestimation of risk, but this was minimised through adjustment in the analysis. Also only 65% of patients and 52% of controls participated in the studyso if the ones who participated were more or less likely to have taken an oral contraceptive it would have an effect on the relative risk. They did compare the people who participated and those who did not with the known confounders of age and residence and only the control groups differed by age with those who participated being more likely to be old. If the older people were more likely to be taking oral

contraceptives it may have affected the results, but this was adjusted for in the analysis to minimise the effect. There is no mention of whether the researchers who administered the interview were blinded so if they were expecting an increased association between oral contraceptives and meningiomas they may have been more likely to find one. In terms of the generalizability of the results it was a multi-centerstudy and could be generalizable to the rest of the population in the United States. If different countries had different incidences of certain receptor subtypes of meningiomas then the relative risk may be affected so care should be taken in generalizing the results out of the country. The results cannot be generalised to the less serious meningiomas which do not need surgery as this study did not include them.

Another study by Michaud D. S. *et al* .(2010) found an OR 3. 61, 95% CI 1. 75–7. 46 comparing current users of the oral contraceptive to never users. (2) This was in a large prospective cohort study called the EPIC cohort study. One flaw in this study was the possibility of diagnostic bias if the users of oral contraceptives were more likely to be investigated and diagnosed with a meningioma which would have increased the association. A strength of this study is the objective measuring of exposure status. They also identified a dose-response trend in pre-menopausal women using an oral contraceptive (HR [95% CI]: 1. 21 [0. 36-4. 06], 1. 55 [0. 53-4. 56], 2. 97 [1. 08-8. 15], 3. 22 [1. 04-10. 0], 3. 60 [1. 00-13. 0] for <1, > 1 –<5, > 5-<10, > 10-<15, > 15 years of use, respectively, p-trend = 0. 01). (2) There have been a few other studies, but none have found a statistically significant risk. (3, 4, 5) These case-control and cohort studies all have a relatively small number of cases

and therefore low power to pick up a true association. In the case-control trials recall bias is difficult to rule out as well as selecting a suitable population that resembles the cases. Furthermore only one of these looked for an association in those on current oral contraceptive use. This calls for a larger study with more power which can pick up an association even if it is quite small.

There are a few findings that point towards a possible association between meningiomas and certain hormones. One of these is the fact that meningiomas are more common in females than males, especially in their reproductive years. (6) Another study has found oestrogen, progestogen and androgen receptors associated with some meningiomas. (7) An older study as well as a more recent case reports indicated that meningiomas become more symptomatic with changes in the menstrual cycle and during pregnancy. (8, 9) These all point towards a possible association between estrogen or progestogen and meningiomas therefore it is an important area to research in order to expand knowledge on this common type of brain tumor.

Study Design:

The type of study design required to answer the aims is a case-control study. As developing a meningioma is a rare outcome, especially in the age group this study is based in, and the exposure of current use of an oral contraceptive is common this makes a case-control study the most efficient way to study this association. Compared to a cohort study they are rapid and cost-effective as cohort studiesrequirea very large population and a long

follow-up period to have enough power to detect an association. A randomised control trial would be more likely to have the results not affected by confounding, but the study would be unethical.

This study must be based overseas in order to increase the number of cases per year. All Australian states and territories have mandatory reporting of all cancers which will allowthe identification of cases. (10) The incidence of meningioma in Australia is approximately 1. 1 to 1. 8 cases per 100, 000 person years with a 2. 6: 1 female to male ratio. (6) For this reason and the fact that the incidence is less frequent in a younger population it requires a multi-centre approach and an extended study period are needed in order to have a sufficient number of cases. The source population will beall females between the ages of 16 and 45 in Victoria, New South Wales and Queensland and cases will be drawn from the cancer registry as they become available. The control group will be population-based and selected from the census. In order to determine the sample size needed for this study the biostatistician will be informed that the study needs to have a large enough power to pick up a 10% increased risk. The result should be statistically significant at 5%. The biostatistician needs to know the expected incidence of the meningiomas in these territories and the proportion of people expected to be using the two types of oral contraceptives. This can be found through state-specific trends or may use the mean and standard deviation from previous years' data. The number of cases this study requires will determine how long the study will run for.

In order to minimise selection bias the criteria for each of the groups needs to be strictly defined. The case criteria is a meningioma of grade I, II or III

according to histological diagnosis by a pathologist. The exposure of current use of an oral contraceptive is defined as taking any oral contraceptive for at least 3 months previous to the diagnosis or in the case of controls 3 months before entry into the study. The exposure status of ever use of an oral contraceptive is defined as if the participant ever taking a single oral contraceptive pill. The population from which the cases arise from are all women between the ages of 16 and 45 in Victoria, New South Wales and Queensland. People will be excluded from the study if they do not speak English, if they have had a previous meningioma, if they have had a brain tumor of unknown pathology, if they have a diagnosed mental health condition, if they have had breast cancer and if they are from a different state or out of the country. Controls will be selected randomly and matched in terms of age, ethnicity, area of residence and socioeconomic status which are all factors that could potentially confound the relationship due to affecting the exposure and the outcome, but not being on the causal pathway between the two. A total of 4 controls will be obtained per case due to the abundance of controls and the relatively small effect of adding any more controls.

The cases and controls will be contacted for participation in the study through mail and if they accept to be in the study a survey will be sent that includes questions related to the confounding factors and the exposure including questions for those who have ever used an oral contraceptive for what duration and which type of oral contraceptive. Information about other possible confounding factors such as smoking status and alcohol use will also be collected. In order to make it more likely that the study participants are

representative of the population the variables that are matched for in each group and the rates of smoking and alcohol use will be compared to the rates in the whole population. These variables will also be compared to those people who dropped out of the study when possible to aid in identifying a systematic difference between those who participated and those who did not. To give an improved chance of patient participation a second survey will be sent to the patients if they do not respond within 2 weeks. If the participants are interviewed then the interviewer will have *a priori* knowledge of the group the participant is associated with and might bias the results towards a significant result.

In order to minimise information bias the cases and controls should be blinded in regards to the aim of the study. To aid in achieving this, the survey sent out to the participants will include questions in regards to other medicines and lifestyle factors such as smoking and drinking. This will prevent the study participants from falsifying their exposure status to agree with what the study is trying to find out and hence would falsely increase the negative risk. One of the largest problems in case control studies is recall bias. To help minimise it a pamphlet with the type of oral contraceptives and what they look like will be included. Everyone in the study gets the same survey and the diagnostic criteria for meningioma are the same in all centres in Australia so information bias from this is unlikely. There also needs to be timely addition of the cases into the cancer registry, otherwise the study will mainly look at the meningioma cases with longer survival. If oral contraceptives are more likely to cause a meningioma with a worse prognosis then the risk will be lower than it actually is.

The results from the study will be presented as:

	Cases (%)	Controls (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Current User of an OC				
Non-Current User of an OC				
Ever use of an OC				
<1 Year Use				
1-5 Year Use				
> 5 Year Use				
Never Use of an OC				
Combined OC				
<1 Year Use				
1-5 Year Use				
> 5 Year Use				
Progestogen OC				

<1 Year Use

1-5 Year Use

> 5 Year Use

The odds ratio reported would be after analysis to take into account that the cases each had 4 individually matched controls. The adjusted OR takes into account that smoking status and alcohol use may be confounders.

This study is ethically sound. It is observational so there is no intervention for the patient. It is also optional and provides no advantage or disadvantage for those participating. Confidentiality will be maintained as only study researchers will have access to the data and none of the data reported in the study will be able to be linked to a specific patient.

The study is feasible, but depends on the sample size that is required. In terms of cost there are no biological tests that need to be performed as all information required is obtained through a survey. The cost of mailing out the surveys and paying staff to collect the information and analyse the data must be considered and budgeted accordingly. One of the advantages of case control studies is looking at multiple exposures hence including other exposures that are of interestcould increase the value of the study and make it more cost-efficient.

Implications:

There are many benefits to this study. As oral contraceptives are already known to increase the risk of other cancers like breast and cervical cancer, if

a causal relationship is found with meningioma, this is another cancer risk that patients must be informed before taking the oral contraceptive. (11) When oral contraceptives will be linked to meningioma, prescribing patterns for those patients who are already at an increased risk for example if they had previous radiation exposure must change. Also patients who have had a previous diagnosis of meningioma would need to strongly consider avoiding taking any oral contraception. These patients would need to find alternate treatment or alternate methods of contraception. If there is an association in the combined oral contraceptive and not the progestogen oral contraceptive this can be recommended to those at risk of developing a meningioma. Another use for determining if there is an associated risk would be through finding treatments or cures for meningiomas. If estrogen or progestogenis found to be related to the development of meningiomas further studies could find a pathway that causes this increased risk and treatments focused on disrupting this pathway may be effective.

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