Oral contraceptives and ovarian cancer risk in pre- and post-menopausal women

Kimberly Casha

A Dissertation Presented to the Faculty of Health Sciences in Part Fulfilment of the Requirements for the Degree of Bachelor of Science (Honours) (Nursing) at the University of Malta

April 2015
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ABSTRACT
Kimberly Casha

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Since their introduction in the late 1950s, oral contraceptives have been used for a multitude of effects, in addition to contraception. Studies have suggested that a protective effect against certain cancers is provided by such method of contraception. However, a negative link between oral contraceptives and cancer still prevails amongst the public. This study aims to analyse whether pre-menopausal and post-menopausal women using oral contraceptives are at a decreased risk of being diagnosed with ovarian cancer, the fourth most common cancer among Maltese females. A systematic search has been carried out to yield valid literature published in English in the last ten years, studying the relationship between any histological type of ovarian cancer in females of all ethnicities using any type of oral contraceptive commercially available. Two systematic reviews, three cohort studies and three case-control studies have been retrieved and critically appraised using the Critical Appraisal Skills Programme tools. It was established that oral contraceptives reduce the risk of ovarian cancer. Risk reduction is increased with an increased duration of use and persists for up to twenty years after stopping oral contraceptives. Additionally, this reduction is not only present in the general population, but also in those carrying the BRCA1 and BRCA2 gene mutations, who are more prone to being diagnosed with ovarian cancer. Despite this protective effect, more research is required to analyse the risk-to-benefit ratio of oral contraceptives, prior to advising their use as a prophylactic method against ovarian cancer, especially in gene mutation carriers. Further local research is also required to evaluate public perception of oral contraceptive use as well as the adequacy of professional knowledge and client education being provided on the subject. Additionally, healthcare professionals as well as potential clients of oral contraceptives should be better educated and made aware of this protective effect.

Keywords: ORAL CONTRACEPTIVES; CONTRACEPTIVE PILL; HORMONAL CONTRACEPTION; OVARIAN CANCER; OVARY CANCER; OVARIAN NEOPLASMS
UNIVERSITY OF MALTA
FACULTY OF HEALTH SCIENCES
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Course: Bachelor of Science (Honours) Nursing

Title of Dissertation: Oral contraceptives and ovarian cancer risk in pre- and post-menopausal women

I hereby declare that I am the legitimate author of this Dissertation and that it is my original work.

No portion of this work has been submitted in support of an application for another degree or qualification of this or any other university or institution of learning.

Signature of Student

Date

Name of Student
DEDICATION

For my parents, for always believing in me and working hard to support my studies.
ACKNOWLEDGEMENTS

I wish to express my gratitude towards Dr. Roderick Bugeja, for his continuous guidance and support throughout the process of this dissertation. I would also like to thank my supervisor, Ms. Antoinette Attard, without whose mentorship and supervision this dissertation would surely not have been possible.
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ABBREVIATIONS

ASHA: American Speech-Language-Hearing Association
BMI: Body Mass Index
CASP: Critical Appraisal Skills Programme
CI: Confidence Intervals
COC: Combined Oral Contraceptives
CONSORT: Consolidated Standards of Reporting Trials
EBP: Evidence-based practice
GP: General Practitioner
HRT: Hormone Replacement Therapy
IUD: Intra-uterine device
NHS: National Health Services
O-E: Observed- Expected
OR: Odds Ratio
POP: Progestogen-only pill
Rr: Rate ratio
RR: Relative risk
RCGP: Royal College of General Practitioners
SE: Standard errors
SIGN: Scottish Intercollegiate Guidelines Network
UK: United Kingdom
UoM: University of Malta
USA: United States of America
WHO: World Health Organisation
Chapter 1:
Introduction
1.1 Introduction

1.1.1 Background information

The first contraceptive pill was created in the late 1950s in Puerto Rico and contained ethinyl estradiol combined with norethynodrel. Such method of contraception was a breakthrough in the field, with an effectiveness of up to 99% (Lakha et al., 2007). In addition to its optimal effectiveness, the contraceptive pill is also relatively easy to use, with its only requirement being to be taken consistently and regularly, on a daily basis at the same time. Existent variations of the contraceptive pill include those containing progestogen-only (POP) and others containing progestogen combined with oestrogen (COC). Limited changes to the original manufacturing of the pill were made throughout the years, with variations in the progestogens and amount of oestrogen used being the most common (Lakha et al., 2007).

The contraceptive pill, as its name implies, is mainly used for contraception, however, it may also be used therapeutically for its secondary effects. Such other effects include a reduction in the incidence of endometrial and colon cancer, “functional ovarian cysts, pelvic inflammatory disease requiring hospitalization, ectopic pregnancy, and iron deficiency anemia” (Dhont, 2011). Additionally, “the pill can be used for the treatment of several gynaecologic disorders such as dysmenorrhea, irregular or excessive bleeding, acne, hirsutism, and endometriosis-associated pain” (Dhont, 2011).

The effectiveness and ease of use of the oral contraceptive pill contribute to its popularity. In 2012, it was estimated that in the United Kingdom (UK), 67.2% of women used the contraceptive pill as their method of contraception, whilst in the United States of America (USA), 44% of women used it (Küçük, Aksu & Sezer, 2012). In the same year, a local study showed that the contraceptive pill (both POP and COC) was the third most popular method of contraception, used by 15.6% of the participants, after the male condom (used by 39.3%) and the withdrawal method (used by 23.7%) (Savona-Ventura, 2012).

Despite its popularity, a certain amount of fear is still associated with oral contraceptive use due to its side-effects and such fear prevents its use in many individuals. In fact, in 1992,
D’Arcangues et al. (as cited in Lakha et al. 2007) found that “fewer than 50% of women continue using oral contraceptives for > 12 months.” Additionally, many women have a lack of information about the proven side-effects of such method of contraception, leading them to having many uncertainties. No recent literature was found related to the topic, and this highlights the need for more research in the field of public perceptions of oral contraceptives. In their research study, Küçük et al. (2012) found that among their 400 participants, an increase in weight, incidence of cancer, infertility, headaches, acne and hirsutism, as well as a decrease in libido were the most common perceived side-effects of the oral contraceptive. No correlation has been found to exist between low-dose oral contraceptives and weight gain (Paxton 1996, as cited in Küçük et al., 2012), infertility, acne and hirsutism (Sanam & Ziba 2011, as cited in Küçük et al., 2012). Conflicting evidence exists regarding the association of oral contraceptive use and decreased libido (Bancroft & Sartorius 1990, as cited in Küçük et al., 2012), whereas cancer risk and oral contraceptive use is subjective to the type of cancer in question (Cibula et al. 2010, as cited in Küçük et al., 2012). Cervical cancer as well as liver cancer have been linked to oral contraceptive use, with cervical cancer having a stronger correlation. It is a proven fact that oral contraceptive use may trigger or increase headaches and are in fact contraindicating in those who suffer from migraines (Allais et al. 2008, as cited in Küçük et al., 2012). In their review, Guida et al. (2010) include tenderness of the breast, nausea and an increased risk of thrombotic events (both venous and arterial) as other proven adverse effects of the oral contraceptive pill. Mood changes, facial pigmentation and decreased menstrual flow were also listed as side-effects by Shakerinejad et al. (2013) in their observational study.

One of the most popular uncertainties about the effects of the oral contraceptive pill is that it increases the incidence of cancer. However, it has been suggested that such pill may contrarily have a protective effect against certain types of cancer, ovarian cancer amongst others. Ovarian cancer is “the most fatal gynaecologic cancer, with 5-year relative survival rates in the United States of 53 percent overall and only 31 percent for women diagnosed with advanced disease” (McGuire et al., 2004). Despite its fatality, its public profile is relatively low when compared to other types of cancer, such as that of the breast. Moreover, methods for prevention and early detection are also very limited. Researchers have proposed multiple models for the etiology of ovarian cancer, with the most popular being
that it is caused by a “cumulative effect of repeated ovulation and exposure of the ovary to high gonadotropin levels. Reproductive factors that interrupt ovulation, such as pregnancies, oral contraceptive use, and lactation, consistently have been associated with a reduced ovarian cancer risk” (Tworoger, Fairfield, Colditz, Rosner & Harkinson, 2007).

1.1.2 Evidence-based practice

One of the most important roles of nurses as outlined in the ‘Maltese Code of Ethics for Nurses and Midwives’ is to educate and promote health. Education of the client cannot be adequately achieved if the nurse is not equipped with recent and relevant evidence-based knowledge. It is therefore the nurse’s duty to keep updated with recent findings relevant to the individual field of practice to ascertain that the standard level of practice is respected and all duties are fulfilled (Nursing and Midwifery Board, 1997). In order to ensure this, the nurse must go beyond that which the layperson thinks is true and consult with relevant literature in order to promote awareness with clients and other health care professionals. Additionally, being aware of recent and valid findings ascertains evidence-based practice (EBP). EBP is defined as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research” (Sackett, 1996). Such practice standard ensures that the patient always receives the best possible care available.

The use of oral contraceptives for its protective effect against ovarian cancer may be beneficial to several groups of people. Those who carry the BRCA1 or BRCA2 gene mutation are perhaps the most obvious, as such gene mutation puts these women at an increased risk of being diagnosed with ovarian cancer. Ovarian cancer is most commonly diagnosed in post-menopausal women (Tworoger et al., 2007), therefore oral contraceptives may be used by older females still in their pre-menopausal stage as a prevention to avoid being diagnosed later on in life. An advantage to using oral contraceptives in the late stages of pre-menopause is that females usually conceive children
in the early and middle stages of adulthood, therefore their use of oral contraceptives would not hinder their ability to conceive, as they would not be trying to do so. Additionally, this protective effect of oral contraceptives may be communicated to clients who wish to use oral contraceptives for their primary use, i.e. contraception, but are afraid as they believe that doing so may increase their risk of ovarian cancer.

1.2 Framing the PICO question

The research question reviewed in this dissertation reads “In pre- and post-menopausal women, does the use of the contraceptive pill decrease the risk of ovarian cancer?”. Such a question was formed using the PICO framework, which encompasses four main components, Population, Intervention, Comparison intervention and Outcome (American Speech-Language-Hearing Association [ASHA], 2012).

The population of interest includes females of all ages that have experienced menarche, therefore being able to use oral contraceptives for their primary effect, that is, contraception. No age-limit is set since although ovarian cancer can be diagnosed at all ages, the age at which oral contraceptives are used and ovarian cancer is most commonly diagnosed differ (Beral, Doll, Hermon, Peto & Reeves, 2008).

The intervention and comparison included in this study are use of oral contraceptives versus no use of oral contraceptives. Type of oral contraceptive used is undefined since literature rarely distinguishes between COC and POP and the two are generally referred to collectively when studying their side-effects. Furthermore, duration of use has been unspecified as studies frequently group varying durations of use together.

The outcome of interest is a decrease in the risk of ovarian cancer through oral contraceptive use. Such outcome would be measured through questionnaires, histological and pathological reports of the population cohorts. No exclusivity to type of ovarian cancer has been applied as these are generally studied collectively in literature. The table below summarizes the PICO elements.
Chapter 1

Introduction

Table No. 1: The PICO Elements

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females in their pre-menopausal and</td>
<td>Use of oral contraceptives</td>
<td>No use of oral contraceptives</td>
<td>Reduction in the incidence of ovarian cancer</td>
</tr>
<tr>
<td>post-menopausal period</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.2.1 Rationale

Ample research has been carried out studying the link between oral contraceptive use and the incidence of ovarian cancer, however uncertainties still prevail among the Maltese population. This might be due to the lack of local literature available on the subject. Additionally, the unethical religious connotation associated with all artificial methods of contraception might also be the cause of such lack of use. The aim of this dissertation is to critically discuss and appraise literature relevant to this topic in order to be able to reach a conclusion that is backed up by evidence, therefore abolishing any misconceptions. Dissemination of the findings to other health care professionals, particularly nurses, would help increase awareness on the topic with clients and the general public, especially since no related research has been carried out in the local setting. Such an increase in awareness would help clients better understand the effects of the oral contraceptive pill as suggested by evidence. Through knowledge, fear of its perceived effects would be decreased, facilitating the use of such a method of contraception with clients who are not planning childbirth, but refrain from using it because of such perceived effects. It would also help decrease the incidence and mortality rates of ovarian cancer among women of all ages.

In the following chapter, the literature selection and identification process is discussed in detail, followed by the critical appraisal of the selected literature in chapter three. Chapter four presents an analysis and detailed discussion of the findings. In the penultimate chapter, recommendations for practice and research are made, especially in relation to the local setting. The final chapter is a conclusion and provides a summary of the dissertation.
Chapter 2:

The Method
2.1 Introduction

The aim of the method is to locate, collect and analyse the relevant studies related to the presented topic that would help form the answer to the PICO question. In order to do this effectively, a systematic review of evidence is crucial, particularly due to the large quantities of evidence usually available. “A systematic review attempts to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question” (Cochrane, 2014). An effective systematic review of evidence starts with a clearly defined question, uses a comprehensive search strategy including both published and unpublished evidence, assess the validity of the findings and results in an effective, unbiased basis for clinical practice whilst identifying gaps in the literature, therefore providing an opportunity for future research (Chalmers, 1993) Hence, this chapter will outline the search strategy and appraisal methods used to analyse the selected studies.

2.2 Formulating the research question

In order to commence with the research process, a clear research topic had to be formulated, thus an online search in the University of Malta (UoM) Online Library’s HyDi platform was carried out for identification of background and foreground information. A manual search at the UoM Health Sciences library was also carried out. After retrieving relevant literature, it was found that the contraceptive pill is not as popular in Malta as it is in other countries (Savona-Ventura, 2012). Further research introduced the idea of misinformation in relation to the adverse effects of such contraceptive method to otherwise potential users (Küçük et al., 2012). Therefore, it was decided that such a research topic would be appropriate for both the local and foreign scene. Initially, the PICO question was formulated to address the effects of the oral contraceptive on the incidence of all types of cancer. The key phrases ‘oral contraceptive’ and ‘cancer’ were input in the UoM Online Library’s HyDi platform but the amount of studies found was unmanageable within the
available timeframe. After further reading of background literature, it was noted that certain literature suggested that contrarily to other cancers (such as that of the cervix), the contraceptive pill might actually reduce the incidence of ovarian cancer in its users, and a PICO question that specifically looks into the relationship between oral contraceptive use and the incidence of ovarian cancer was formulated. Such a refinement in the PICO question was made to enable a more thorough analysis of the literature available on the specific research topic that would allow a more comprehensive systematic review. Table 2 represents the PICO elements used in this systematic review.

**PICO Question:** *In pre- and post-menopausal women, does the use of the contraceptive pill decrease the risk of ovarian cancer?*

**Table No. 2 PICO Framework**

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females in the pre-menopausal and post-menopausal period</td>
<td>Use of oral contraceptives</td>
<td>No use of oral contraceptives</td>
<td>Reduction in the incidence of ovarian cancer</td>
</tr>
</tbody>
</table>

**2.3 Literature Search**

After formulating the research question, an online search was carried out. This was not done before a list of keywords and key phrases that would help locate and retrieve literature relevant to the research topic was generated. Selection of keywords prior to carrying out the search ensures a comprehensive search that allows for no gaps in the literature. This also helps reduce the number of irrelevant hits generated in the search (Garrie, 2012). The keywords and key phrases used were ‘oral contraceptive’, ‘contraceptive pill’, ‘hormonal contraception’, ‘ovarian cancer’, ‘ovarian ca’, ‘ovarian neoplasm(s)’, ‘ovary cancer’, ‘ovary ca’, ‘ovary neoplasm(s)’ as outlined in Table 3.
TABLE NO. 3: KEYWORDS

<table>
<thead>
<tr>
<th>PICO element</th>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention- Contraceptive pill</td>
<td>Oral contraceptive</td>
</tr>
<tr>
<td></td>
<td>Contraceptive pill</td>
</tr>
<tr>
<td></td>
<td>Hormonal contraception</td>
</tr>
<tr>
<td>Outcome- Decreased risk of ovarian cancer</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td></td>
<td>Ovarian ca</td>
</tr>
<tr>
<td></td>
<td>Ovarian neoplasm(s)</td>
</tr>
<tr>
<td></td>
<td>Ovary cancer</td>
</tr>
<tr>
<td></td>
<td>Ovary ca</td>
</tr>
<tr>
<td></td>
<td>Ovary neoplasm(s)</td>
</tr>
</tbody>
</table>

The databases searched from the UoM Online Library’s HyDi platform include Cochrane Central Register of Controlled Trials (EBSCO), CINAHL Plus with Full Text (EBSCO), BioMed Central, Academic Search Complete (EBSCO), Database of Abstracts of Reviews of Effects (EBSCO), AgeLine (EBSCO) and the Cochrane Database of Systematic Reviews (EBSCO). Another search was carried out using Google Scholar, with similar results being generated as in the HyDi platform, therefore the search was continued using the HyDi platform alone. The articles retrieved up to this point started to mention the author Ness more frequently than others, therefore her works were sought after more vigorously. Table 4 provides a summary of the results generated using various search terms in the UoM Online Library’s HyDi platform.
### TABLE NO.4: HYDI SEARCH

<table>
<thead>
<tr>
<th>Searches</th>
<th>Keyword/ Key phrase</th>
<th>Total Hits Generated</th>
<th>Possibly Relevant Hits Generated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search 1</td>
<td>Oral contraceptive</td>
<td>6,655</td>
<td>Not manageable</td>
</tr>
<tr>
<td>Search 2</td>
<td>Ovarian cancer</td>
<td>42,934</td>
<td>Not manageable</td>
</tr>
<tr>
<td>Search 3</td>
<td>Ovarian neoplasms</td>
<td>13,296</td>
<td>Not manageable</td>
</tr>
<tr>
<td>Search 4</td>
<td>Contraceptive Pill</td>
<td>1,453</td>
<td>Not manageable</td>
</tr>
<tr>
<td>Search 5</td>
<td>Contraceptive pill AND ovarian cancer</td>
<td>40</td>
<td>21</td>
</tr>
<tr>
<td>Search 6</td>
<td>Oral contraceptive AND ovarian cancer</td>
<td>394</td>
<td>24</td>
</tr>
<tr>
<td>Search 7</td>
<td>Ovary cancer</td>
<td>272</td>
<td>17</td>
</tr>
<tr>
<td>Search 8</td>
<td>Ovary neoplasms</td>
<td>77</td>
<td>0</td>
</tr>
<tr>
<td>Search 9</td>
<td>Ovarian ca</td>
<td>45</td>
<td>2</td>
</tr>
<tr>
<td>Search 10</td>
<td>Ovary ca</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

As the table clearly illustrates, when keywords were input separately, a large number of hits were generated, the majority of which were irrelevant to the topic of interest, i.e. they did not study the two components of interest together (oral contraceptives and ovarian cancer). The large amount of results obtained meant that reading all articles retrieved from the search would have been too time-consuming for the timeframe of this critical appraisal, therefore it was decided that in each search, the results would be sorted by relevance to the input keywords, meaning that the most relevant ones are displayed first. This enabled better management of the large amount of hits obtained, as the first number of pages displaying the most relevant studies could be analysed in detail while those towards the end of the results list were omitted as they displayed studies that were either duplicate or highly irrelevant to the search.
When two keywords were combined, fewer studies were retrieved and these were generally more relevant to the topic of interest. Combining all possibly relevant entries yields 148 hits. After reading the titles and abstracts of these articles, papers that were either duplicate, used the same cohort data of main studies for reanalysis or did not include both search components (oral contraceptives and ovarian cancer) in their analysis and present their respective results were eliminated, after which a total of twenty-five studies were left. Applying inclusion and exclusion criteria, (discussed in the next section) resulted in eight valid studies that would be critically appraised in the next chapter. Reference lists of these eight studies were analysed in an effort to retrieve more valid studies, however none were found. Figure 1 below summarizes the research process.

**Figure No. 1: The Literature Search**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65,170 hits generated in total with individual keywords</td>
</tr>
<tr>
<td>2</td>
<td>Unmanageable number of hits, therefore keywords were combined with Boolean operators</td>
</tr>
<tr>
<td>3</td>
<td>148 possibly relevant hits</td>
</tr>
<tr>
<td>4</td>
<td>123 entries eliminated by reading title and/or abstract due to irrelevance, duplicated studies, use of same cohort data in different analyses</td>
</tr>
<tr>
<td>5</td>
<td>25 studies selected for in-depth validity assessment</td>
</tr>
<tr>
<td>6</td>
<td>Inclusion and exclusion criteria applied, resulting in 8 valid and relevant studies</td>
</tr>
</tbody>
</table>

### 2.4 Inclusion and Exclusion Criteria

Studies would only be eligible if they were available as full text online for free. Whilst the majority of the generated articles were available in this format, others were not. These were noted and searched for using Google as the search engine of choice. However, no further
articles were retrieved. Studies would also be published in English in the last ten years. Such publication year limit was established since with the research question at hand, a long follow-up means more robust and valid literature. Therefore, extending the publication year limit beyond ten years would mean that the study would have been initiated over forty years ago, and most oral contraceptive preparations available then are no longer on the market. Informal literature such as opinion articles were not considered for this search. The population for the studies could be of any ethnicity, in fact the studies chosen include participants of Caucasian and African descent. No exclusion criteria were applied for the type of contraceptive pill used (whether POP or COC) and the duration or age of usage. Furthermore, no exclusion criteria were applied for the type of ovarian cancer (whether epithelial, germ cell or stomal) and the age at diagnosis. Such limitation in the number of exclusion criteria used is due to the fact that many studies do not include one type of oral contraceptive or ovarian cancer exclusively. Furthermore, very few papers define their population by ethnicity or age at diagnosis, and doing so would have limited my search extensively. Papers that studied other types of cancer or contraceptive methods in addition to those of interest were also included given that they provided a thorough analysis of the topic of interest.

**Table No. 5: Inclusion Criteria**

<table>
<thead>
<tr>
<th>Inclusion criterion</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free full text online</td>
<td>To avoid purchasing papers that may prove irrelevant to the topic of interest</td>
</tr>
<tr>
<td>Published in English</td>
<td>To avoid any misinterpretations in translation</td>
</tr>
<tr>
<td>Published within last ten years</td>
<td>To ensure studies are current and valid</td>
</tr>
</tbody>
</table>
2.5 Critical Appraisal

“Critical appraisal is the process of carefully and systematically examining research to judge its trustworthiness, and its value and relevance in a particular context” (Burls, 2009). It is an essential skill to all health care professionals as it enables evidence-based practice through identification of reliable, valid, accurate and unbiased literature. Identification of such literature ensures that informed healthcare decisions are made that maintain the best interest of the patient at heart. Critical appraisal tools are frequently used for a more thorough analysis of the studies at hand. Various critical appraisal tools are available, such as that by the Scottish Intercollegiate Guidelines Network (SIGN), the Critical Appraisal Skills Programme (CASP) and the Consolidated Standards of Reporting Trials (CONSORT). The CASP (Appendix 1) provides various tools that can be used for the critical appraisal of literature according to the design implemented in each study. These critical appraisal tools are perhaps one of the most utilised, used by researchers worldwide.

Such popularity can be attributed to various reasons, one of which is the fact that the said tools are all available online for free in their full versions. The CASP also offers a number of different tools specifically designed for different designs utilised in the study at hand, therefore critical appraisal can be more thorough and specific. Each CASP tool was developed by a multidisciplinary team of professionals, tested by non-expert health care professionals and modified, therefore ensuring its efficiency and ease of use. (National Collaborating Centre for Methods and Tools, 2011). Furthermore, the tools are continuously being refined and updated. Such tools also allow systematic appraisal of the studies, with the questions divided into three sections, analysing internal and external validity of the studies. Section A analyses the validity of the study, Section B evaluates the results obtained and Section C considers their relevance within the local context. One of the few notable limitations of the CASP tools is that no scoring system is available within the checklist. The inclusion of such score would make it easier for researchers to rank the studies at hand into a hierarchy using a common scoring system, particularly when a large amount of studies are being appraised.
For this systematic review, the chosen case-control studies were appraised using the CASP Case-Control Study, which enabled the identification of reliable and valid papers to be included in this study. A systematic appraisal was carried out through a series of eleven questions that analyse vital aspects of the literature such as element of bias, appropriateness of methodology chosen, precision of the results and their applicability to the local scenario (CASP, 2013a). Furthermore, the CASP Cohort Study and CASP Systematic Review tools were used to critically analyse the remaining studies using the respective study designs. The CASP Cohort Study entails twelve questions that are applied to the study in question. These questions analyse the clarity of the research question, the longevity of the follow-up and the implications of the results in practice (CASP, 2013b). Similarly, the CASP Systematic Review uses ten questions analysing the relevance of the included studies, the rigour with which they have been assessed and the outcomes considered (CASP, 2013c).

In the next chapter, the CASP tool checklists are utilised for a thorough evaluation and critical appraisal of the eight key papers chosen to be included in this literature review.
Chapter 3:
Critical Appraisal of the Literature
3.1 Introduction

Following the identification of relevant papers using inclusion and exclusion criteria, as outlined in the previous chapter, analysis of such papers was necessary for the selection of key studies to be included in the critical appraisal. In this chapter, the selected papers are appraised more thoroughly using the CASP tools.

3.2 Hierarchy of Evidence

Evidence based practice relies upon good clinical judgment, the best available literature and the patient’s individual values (Petrisor & Bhandari, 2007). Thus, literature must be ranked in order of validity for the best available literature to be identified. Such ranking is done through use of a hierarchy of evidence model, such as that developed by the Joanna Briggs Institute (2013). Figure two below is a graphical representation of the model.
This model was chosen as it is specific to prognostic research questions, thus being more detailed and specific to the research question at hand. Other general hierarchies of evidence rank the research methods used in the literature chosen for this study (mainly case-control and cohort studies) in the lowest rankings, which is not fully accurate. The research method used depends upon the type of question being asked. For ethical reasons, randomised control trials, which are usually at the top of such hierarchies, would not have been possible to conduct in order to address the research question at hand.

This model has five levels, each having sub-levels. At the top of this hierarchy are inception cohort studies since they follow their participants early on, usually shortly after
diagnosis or exposure, for a longer and more complete follow up. Such studies are further sub-divided, with systematic reviews of inception cohort studies atop singular inception studies. The next level entails studies of all or none. Such studies have dramatic exposures to which all or none participants experience the outcome, therefore providing an unbiased representation of the prognostic effect. Such studies are sub-divided as the previous level. Cohort studies are ranked in the third level of this hierarchy. Cohort studies identify participants and follow them to observe how an exposure that cannot be experimentally controlled, affects their outcome over time. Systematic reviews of cohort studies are ranked on top of single studies.

Similarly, case series, case-control studies and historically controlled studies are ranked fourth. In this study, only literature with a case-control methodology was used. Case-control studies compare one cohort with a specific diagnosis, to another with no diagnosis, in their history of exposures to determine their effect on the outcome of interest. Systematic reviews of such studies are atop singular studies. The final level entails expert opinion and bench research and is further sub-divided in systematic reviews of expert opinion, expert consensus and bench research or single expert opinion respectively.

Studies ranked lower in the hierarchy might still be utilised for practice, however more attention should be given to the methodology and element of bias to assess their reliability.

3.3 Critical appraisal of the studies

In this section, the validity of the results of the articles and their application in the local context are analysed as outlined in sections A and C of the CASP tools. Studies are grouped according to their methodology and the respective critical appraisals are presented in order that complements their rank in the hierarchy of evidence, starting with the ones most valid.
### 3.3.1 Critical appraisal of systematic reviews with meta-analysis

**Table No. 6: Systematic reviews**

<table>
<thead>
<tr>
<th>Authors (publication year)</th>
<th>No. of studies/ no. of participants</th>
<th>Country</th>
<th>Population studied</th>
<th>Interventions measured</th>
<th>Outcomes evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beral, V., Doll, R., Hermon, C., Peto, R., &amp; Reeves G. (2008)</td>
<td>45/ 110,000</td>
<td>Multicentre</td>
<td>Older adult females diagnosed with malignant non-/epithelial ovarian cancer (cases), healthy females (controls)</td>
<td>-Ever oral contraceptive use&lt;br&gt;-Duration of oral contraceptive use&lt;br&gt;-Age at first and last oral contraceptive use&lt;br&gt;-Calendar year at first and last oral contraceptive use</td>
<td>-Ovarian cancer risk in ever versus never use&lt;br&gt;-Ovarian cancer risk by duration of use/time since ceasing use&lt;br&gt;-Ovarian cancer risk by age at first use/calendar year of use&lt;br&gt;-Ovarian cancer risk by tumour histology&lt;br&gt;-Ovarian cancer risk by country</td>
</tr>
<tr>
<td>Iodice, S., Barile, M., Rotmensz, N., Feroce, I., Bonanni, B., Radice, P., Bernard, L., Maisonneuve, P., &amp; Gandini, S. (2010)</td>
<td>18/13,627</td>
<td>Multicentre</td>
<td>Adult females having a BRCA1/BRCA2 gene mutation (cases), BRCA1/BRCA2 non-carriers (controls)</td>
<td>-Ever oral contraceptive use&lt;br&gt;-Duration of oral contraceptive use&lt;br&gt;-Age at first oral contraceptive use&lt;br&gt;-Time since ceasing oral contraceptive use</td>
<td>-Ovarian cancer risk in ever versus never use&lt;br&gt;-Ovarian cancer risk by duration of use&lt;br&gt;-Ovarian cancer risk by type of gene mutation</td>
</tr>
</tbody>
</table>
Two relevant studies having a systematic review with meta-analysis design were identified, details of which have been summarized in Table 6 above. Beral et al. (2008) assessed the longevity of the protective effect against ovarian cancer that oral contraceptive use provides. Iodice et al. (2010) examined whether oral contraceptives offer the same protective effect in women carrying a BRCA1 or BRCA2 gene mutation, as it does in the general population. Such women have an increased risk of developing ovarian and breast cancer due to their mutated gene.

The first section of the CASP tool assesses the validity of the results by examining the question asked and the appropriateness of the studies chosen for review. Both studies had a clear and focused question, Beral et al. (2008) reviewed studies assessing the outcome of interest in female adults diagnosed with malignant epithelial or non-epithelial ovarian cancer (as cases) and in healthy female adults as their controls. Iodice et al. (2010) considered interventions and outcomes in a focused population, i.e. females with a BRCA1 or BRCA2 gene mutation as cases and females without the mutated gene as controls. While such focus in population makes the results less generalisable, its findings are valuable as they confirm the protective effect in gene mutation carriers, who are at a higher risk of being diagnosed with ovarian cancer.

In the two reviews, papers with a case-control or cohort study design were chosen and all included studies addressed the review question by having the appropriate population, interventions and outcomes. In Beral et al.’s study (2008) such papers were identified through an electronic search using Medline, Embase and PubMed databases, discussion with the authors’ colleagues also rendered some valid articles. Studies were eligible if they included at least 100 women with ovarian cancer and extensive information about their reproductive history and oral contraceptive use was available. Forty-five studies were included and their respective principal investigators were invited to participate for further verification and analysis of data. Iodice et al. (2010) retrieved studies using the MEDLINE search strategy on PUBMED, EMBASE and Ovid MEDLINE databases. Keywords were combined to yield relevant studies. Additionally, the most cited articles on the topic were identified through the ISI Web of Knowledge Science Citation Index Expanded as well as from the reference lists of valid studies. Extraction and analysis of data from the studies of
interest was performed independently by two investigators, compared and adjusted for any discrepancies. For studies to be relevant, gene mutation carriers in the population had to be tested for verification of their carrier status.

The search strategy adopted by both reviews included in this critical appraisal used multiple databases to extract their relevant studies. Additionally, they used other methods of searching for literature, such as reference lists and discussion with professionals. This widens the range of articles available for retrieval, strengthens the search strategy and makes the findings more robust. Beral et al.’s findings (2008) are more robust as they included more than double the number of studies and consisted of a population nearly ten times that of Iodice et al.’s study (2010).

Beral et al. (2008) used the ‘Observed- Expected’ (O-E) formula to obtain odds ratio (OR) and their p-values. OR are used to quantify how strongly the presence or absence of an outcome is in relation to the presence or absence of an exposure within a defined population. A p-value, on the other hand, indicates the statistical significance of an observation. A significance level is set before the commencement of a study, as a threshold. If the p-value is equal to or smaller than the significance level, then the null hypothesis is rejected and the alternative hypothesis is declared true (Cochrane, 2011). Using O-E formula is favourable as assumptions about the precise forms of any relations in the data are avoided, thus ensuring accuracy. When two groups were compared relative risks (RR) and their corresponding standard errors (SE) and confidence intervals (CI) were obtained using the one-step method, which is the favoured method to approximate solutions that do not change rapidly, as in this case. RR are ratios of the probability of the occurrence of an event by comparing the risk between two exposures. SE measure the accuracy with which a sample represents a population. CI describe the uncertainty associated with a sample estimate of a population parameter (Cochrane, 2011). With this method, valid comparisons between two exposure groups are possible, even if neither group was the baseline.

Iodice et al. (2010) used the Chi-square test to assess for heterogeneity in their results. This test analyses the likelihood with which any observed differences between two groups arose by chance rather than by heterogeneity (Fisher and Yates, 1963). A p-value of ≤0.10 was set, which means that there is a 10% risk that the results may be attributed to chance alone,
indicating a high degree of validity in the results. Meta-regression was also used to examine the influence of confounding variables between studies on the outcome results. This method analyses heterogeneity between studies to determine the validity of the results, however it requires extensive detailed information for every study included in the meta-analysis, which may not always be available. Data analysis and presentation was appropriate in both studies, combining similar results for a better discussion of the outcomes, whilst presenting individual studies’ results for a clearer analysis. Beral et al. (2008) took additional measures to enhance the accuracy of the results by centrally collating data to enable similar definitions across studies, centrally categorising tumors and stratifying results for more homogenous comparisons.

Bias was minimised in both studies, Beral et al. (2008) ensured that any missing data were gathered by the respective study investigator as were data about the histology of ovarian tumours in the cases, thus allowing for a more thorough and complete data analysis. Any inconsistencies in data were also discussed and amended with study investigators. Participants of cohort studies were incorporated using a nested case-control design. Random controls were matched with cases for key variables such as age at diagnosis and region of residence prior to analysis. Such variation of the case-control design allows for a more standardised comparison of cases and controls, thus increasing their homogeneity and preventing selection bias.

Robustness of the studies were increased by performing sensitivity analyses for classification of participants by calendar year of oral contraceptive use. Sensitivity analysis eliminates uncertainties in the review process, thus increasing the robustness of the findings (Cochrane, 2011). In this case, such uncertainties include age of the participants at oral contraceptive use as well as the preparation of the contraceptive used, which varies according to calendar year. Furthermore, analysis of data was stratified by key confounding variables (such as age and parity) to ensure fair comparison of cases and controls. In Iodice et al.’s study (2010), homogeneity was increased through sensitivity analyses for heterogeneous exposures, adjusting data to a maximum number of confounding factors, and evaluation for publication and survival bias through funnel plots and sensitivity analyses respectively. All these measures ensure that the results obtained are valid and reliable.
The results of both reviews can be utilised in the local setting, mainly due to the fact that the population of the studies was exclusively or majorly European, therefore having similar lifestyles and cultures as well as availability of similar oral contraceptives to both populations. Iodice et al.’s study (2010) features a focused population, therefore limiting the extent to which its findings can be applied to the general population, however this does not mean that they are less valuable as they can be applied to gene mutation carriers, who have increased risk factors for ovarian cancer. Furthermore, whilst the findings of both studies can be applied to the local setting, they are not appropriate for global application, especially in underdeveloped countries, where the level of healthcare provided may be inferior and the use of oral contraception is less common.

The two studies used appropriate methods in extracting papers for their review, and analysed such papers with rigour and reason. Both studies have thus been chosen to contribute to the evidence base of this critical appraisal after completing the critical appraisal test as outlined in the CASP tool with success.
### 3.3.2 Critical appraisal of cohort studies

<table>
<thead>
<tr>
<th>Authors/ publication year</th>
<th>No. of participants</th>
<th>Country</th>
<th>Population studied</th>
<th>Interventions measured</th>
<th>Outcomes evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessey M., &amp; Painter, R. (2006)</td>
<td>17,032</td>
<td>UK</td>
<td>25-39 year old married British females</td>
<td>-Ever oral contraceptive use  -Type of oral contraceptive used  -Duration of oral contraceptive use  -Time since last oral contraceptive use</td>
<td>-Cancer risk in ever versus never use  -Cancer risk by duration of oral contraceptive use  -Cancer risk by time since last oral contraceptive use</td>
</tr>
<tr>
<td>Hannaford, P.C., Selvaraj, S., Elliott, A.M., Angus, V., Iversen, L., &amp; Lee, A.J. (2007)</td>
<td>45,950</td>
<td>Married British females (mean age 29 years), mainly caucasian</td>
<td>-Ever oral contraceptive use  -Duration of oral contraceptive use  -Time since last oral contraceptive use</td>
<td>-Cancer risk in ever versus never oral contraceptive use  -Cancer risk by duration of oral contraceptive use  -Cancer risk by time since last oral contraceptive use</td>
<td></td>
</tr>
</tbody>
</table>
Three valid cohort studies were identified. Table 7 gives a summary of their details. Vessey and Painter (2006) analysed the relationship between oral contraceptive use and the incidence of ovarian, breast, cervical and endometrial cancer, while Hannaford et al. (2007) aimed at examining the risks or benefits on cancer associated with oral contraceptive use. Tworoger, Fairfield, Colditz, Rosner and Hankinson (2007) examined the association between oral contraceptive use and the duration of protection against ovarian cancer, as well as the effect other contraceptive methods and infertility have on the risk of said cancer. All three studies addressed a clearly focused issue reflected in the population, risk factors and outcomes studied, therefore increasing the validity of their results and the appropriateness of their methodology, according to the CASP tool.

Vessey and Painter (2006) recruited over 17,000 individuals for their study. All were 25-39 year old married British females currently using oral contraceptives, diaphragm or intra-uterine device (IUD) for at least five months. The participants were recruited from family planning clinics across England and Scotland between 1968 and 1974 as part of the Oxford Family Planning Association contraceptive study. Hannaford et al. (2007) used data from the Royal College of General Practitioner’s (RCGP) oral contraceptive study. Briefly, recruitment began in May 1968 and occurred over a period of fourteen months, during which over 1,400 general practitioners (GP) throughout the UK enlisted 23,000 users of oral contraceptives and 23,000 non-users. All participants were married and Caucasian and had a mean age of twenty-nine years old. Tworoger et al. (2007) used data from over 100,000 participants in the US Nurses’ Health Study with a twenty-eight year follow-up (1976-2004) which was gathered and analysed for the outcomes of interest. Participants were recruited in 1976, all were 30-55 years of age, married registered American nurses. Table 8 below summarizes the processes used.
Table No. 8: The recruitment process

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of participants</th>
<th>Inclusion criteria</th>
<th>Year of recruitment</th>
<th>Mode of recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessey and Painter (2006)</td>
<td>17,000</td>
<td>-25-39 years old -British -Married -Currently using OC, diaphragm or IUD for at least 5 months</td>
<td>1968-1974</td>
<td>Family planning clinics in England and Scotland</td>
</tr>
<tr>
<td>Hannaford et al. (2007)</td>
<td>46,000</td>
<td>-Married -Caucasian -Attending participating GP</td>
<td>1968-1970</td>
<td>GP participating in RCGP study</td>
</tr>
<tr>
<td>Tworoger et al. (2007)</td>
<td>100,000</td>
<td>-30-55 years old -Married -American -Registered nurses</td>
<td>1976</td>
<td>Participants in US Nurses’ Health Study</td>
</tr>
</tbody>
</table>

While all three studies had a large population, the sizes differ greatly. Tworoger et al.’s (2007) population was the largest and therefore had the most robust findings. The three studies based the recruitment of their participants on similar inclusion and exclusion criteria, which were all highly specific. This increases the comparability of the findings to each other. However, Vessey and Painter (2006) recruited their participants from family planning clinics. According to the authors this has affected their population as participants were generally more health conscious and came from a higher social class, and this may reduce the extent to which the findings can be applied to the general population. Hannaford et al. (2007) had no specific age range, and their research question was thus less focused, however the mean age of the participants was within the range of the other two studies and the results were therefore still comparable. Furthermore, the studies had a wide age range for their participants, increasing the applicability of the findings to the general population. Tworoger et al.’s (2007) participants were considerably older than those of the other two studies and this may have influenced the results, particularly because ovarian cancer is usually diagnosed in post-menopausal women.
Vessey and Painter (2006) interviewed participants at recruitment about their contraceptive, medical and child-bearing history together with other anthropometric and socioeconomic data. Following the interview, individuals were flagged in the National Health Service (NHS) central registries for automatic notification of cancer registrations or death. Annual follow-up in the form of interviews by research assistants at the clinic, the participants’ homes, by post or phone continued until the participants were forty-five years of age or until mid-1994. After that, follow-up continued through NHS central registries until 2004. Any cases of cancer notified through NHS central registries or annual follow-ups were confirmed by hospital case summaries for further clarification. The nature of the interview carried out during follow-up was not specified, and this may have introduced a source of bias, especially if open-ended questions were asked, resulting in subjective answers. Furthermore, the level of expertise of the research assistant was also not indicated, and this determines the quality of the follow-up.

In Hannaford et al.’s study (2007) baseline information about medical and reproductive history, smoking and social class was obtained at recruitment through an interview. Follow-up occurred through information supplied by the GP every six months about any changes in contraception, pregnancies, new illnesses (including cancer) and any surgical interventions occurring in the participants. Additionally, in mid-1970s all remaining participants (about 75%) were flagged at NHS central registries to enable automatic notification of cancer or death, thus creating two separate datasets for the same participants. Follow-up by the GP continued for twenty-eight years (until the end of 1996), until the participant left the area of the recruiting practitioner, oral contraceptives were obtained from an external source, the GP left the study, or due to death. Follow-up through NHS central registries occurred until the end of 2004 or diagnosis of the first relevant cancer. Creating two datasets may have introduced confusion and uncertainties, however it could have also proved beneficial as comparison between the two datasets increases the validity of the collected data. Data from the GP follow-up dataset is less valid than the main dataset supplied by NHS central registries due to the large proportion of participants lost during follow-up and the subjectivity of the data provided, particularly because no reference to the use of a protocol for follow-up by the GP was made.
In Tworoger et al.’s study (2007) data was gathered through mailed questionnaires at recruitment, asking about age, anthropometric data, oral contraceptive history, risk factors for cancer, infertility and reproductive history. Biennial questionnaires were mailed for follow-up, checking for use of oral contraceptives, other contraceptive methods (tubal ligation, diaphragm, rhythm method, condoms, IUD, foam, vasectomy) and new diagnoses. Following diagnosis or death, pathology reports and medical records were obtained and reviewed by a gynaecologic pathologist who was blinded to exposure status of the individual, for diagnosis confirmation. Such blinding prevented performance bias and increased reliability of the findings. The nature of the questionnaires used was not specified, and this determines the validity of the data obtained, as an element of subjectivity and interpretation bias could be present. In Vessey and Painter’s (2006) and Hannaford et al.’s study (2007), follow-up was maintained via central registries, thus enabling automatic notification of diagnosis and eliminating detection bias, increasing the reliability of the data.

In the three studies, standardised incidence rates were calculated using the corresponding formula. Incidence rates measure the frequency with which a disease occurs over a period of time and is obtained by dividing the number of new cases by the number of persons at risk during the same period. Using this measure has the advantage of being able to compare incidence within the study population with the incidence in the general population, thus assessing whether the results obtained were a product of chance rather than heterogeneity. Vessey and Painter (2006) also performed tests of significance to test their hypotheses. Such tests are used to generalise the findings of a study to the general population, however caution should be applied as misleading results can be obtained should the population size used be inappropriate. In this case, the population size was modest, therefore such test was appropriate. Tworoger et al. (2007) have also estimated their incidence rates in terms of person-years, meaning the amount of ‘at risk’ time each person contributes to the calculation. This test is often impossible to carry out, therefore an estimate of person-years is made instead. Carrying out this test enables the authors to account for participants lost during follow-up, thus increasing the accuracy of their findings.
All three studies identified the majority of important confounding factors. Confounding factors are variables that may influence the outcome, but are not part of the risk factors of interest (Cochrane, 2011). Such confounding factors include: age, body mass index (BMI), parity, smoking habits, use of hormone replacement therapy (HRT) and social class (Vessey and Painter 2006, Hannaford et al. 2007 and Tworoger et al. 2007). All three studies missed family history of ovarian cancer as a potential confounding factor, this may have influenced the results and decreased their validity. All data were adjusted for the identified confounding factors, however, only Tworoger et al. (2007) identified the method used for such adjustment, thus the data adjustment performed by the other two authors is not clear. Follow-up in the studies was long enough and complete. Vessey and Painter (2006) and Hannaford et al. (2007) both followed their population for thirty-six years, while Tworoger et al.’s (2007) follow-up lasted twenty-eight years. While both durations are long enough to ensure robustness and validity of the findings, Tworoger et al.’s may be less robust by comparison. Validity is, however, equal as the findings are very similar in all three studies. In Hannaford et al.’s study (2007), follow-up was less complete then desired, as GP follow-up ceased after 1996. Although comparison of the two datasets after 1996 is not possible, such limitation with this type of follow-up is expected due to change in residence location and consulting GP through the years.

All authors took measures to eliminate bias. Vessey and Painter (2006) eliminated participants using a diaphragm or IUD with a history of oral contraceptive use to prevent confusion and increase homogeneity. Furthermore, participants who were known to have been previously diagnosed with the same cancer prior to recruitment and had relapsed during follow-up were omitted from the study. This was done to avoid survival bias and due to the fact that such individuals had a higher risk of being diagnosed with cancer, thus affecting the results. Hannaford et al. (2007) compared information about new diagnoses from GP and central registries for clarity, and agreement was reached in the majority of cases, proving the validity of the collected data. Tworoger et al. (2007) excluded participants if they had a history of any cancer or bilateral oophorectomy prior to recruitment, avoiding survival bias.
The results of Vessey and Painter’s study (2006) and Hannaford et al.’s study (2007) are especially valuable to the local population as both included British participants, meaning similar ethnic and lifestyle factors as well as similar oral contraceptive formulations available due to similar formularies. The studies imply that oral contraceptives provide a protective effect against ovarian cancer. Furthermore, both studies concluded that within their population, oral contraceptives had a beneficial effect against the overall cancer risk.

Limitations of these studies include their timing, as the majority of oral contraceptive use occurred in the 1970s and 1980s, when a much higher dose of oestrogen was used in oral contraceptives compared to the present standards and this may have influenced the significance of the findings. Such limitation is acknowledged by Vessey and Painter (2006) and by Hannaford et al. (2007) but not by the other author. Neither study adjusted their data for family history as a potential confounding factor. This might have influenced the results as those with a family history have an increased risk of ovarian cancer, therefore more cases would have been diagnosed within the study. Both Hannaford et al. (2007) and Tworoger et al. (2007) acknowledged such limitation. In Hannaford et al.’s study (2007), a large proportion of participants were lost to follow-up (about 33%), thus resulting in an incomplete follow-up which might have introduced attrition bias. This limitation is common in prospective cohort studies due to their long follow-up. The authors have acknowledged such limitation and stated that women lost to follow-up had similar ovarian cancer risks as those that remained in the study, thus results were unaffected. Additionally, participants were excluded if they suffered from any chronic condition, this favoured follow-up as a lower mortality rate was observed among the cohort, however, this has also limited the generalisability of the results, especially since chronic conditions are becoming more common in high-income countries (World Health Organisation [WHO], 2005).

All three studies have been retained to form part of the critical appraisal, following rigorous evaluation through the CASP tool, which confirmed their validity and reliability.
### 3.3.3 Critical appraisal of case-control studies

**Table No. 9: Case-Control Studies**

<table>
<thead>
<tr>
<th>Authors (publication year)</th>
<th>No. of cases/controls</th>
<th>Country</th>
<th>Population studied</th>
<th>Interventions measured</th>
<th>Outcomes evaluated</th>
</tr>
</thead>
</table>
- Type of oral contraceptive used
- Frequency and duration of use
- Reason for use | -Ovarian cancer risk in ever versus never use
-Ovarian cancer risk according to parity and oral contraceptive use |
| Greer, J.B., Modugno, F., Allen, G.O., & Ness, R.B. (2005) | 608/926               | USA     | 20-69 year old females with confirmed epithelial ovarian cancer (cases) and healthy individuals (controls) | -Ever use of oral contraceptives
- Type of oral contraceptive used
- Reason for starting and stopping use
- No. of episodes of oral contraceptive use
- Duration of use | -Ovarian cancer risk in ever versus never use
-Ovarian cancer risk by duration of use
-Ovarian cancer risk by no. of episodes of use
-Ovarian cancer risk by reason for stopping oral contraceptives |
- Duration of oral contraceptive use | -Ovarian cancer risk in ever versus never use
-Ovarian cancer risk by duration of oral contraceptive use, according to germ-line status |
Three valid case-control studies were identified and their details have been summarized in Table 9. Ness, Dodge, Edwards, Baker and Moysich (2011) studied the effects of different contraceptive methods, including oral contraceptives, on the risk of ovarian cancer. This was done by comparing ≥ twenty-five year old females diagnosed with primary epithelial ovarian, peritoneal or Fallopian tube cancer (as cases) with healthy female adults of the same age (as controls). Greer, Modugno, Allen and Ness (2005) wanted to ascertain whether short-term use of oral contraceptives provides a protective effect against ovarian cancer. Hence, they compared twenty to sixty-nine year old females diagnosed with epithelial ovarian cancer (as cases) with healthy females (as controls) in their use of oral contraceptives. McGuire et al. (2004) examined the relation of contraceptive and reproductive history to ovarian cancer risk in carriers and non-carriers of BRCA1 gene mutations by comparing twenty to sixty-four year old females diagnosed with invasive epithelial ovarian cancer (both carriers and non-carriers of BRCA1 mutation) with healthy females (non-carriers) as controls. According to the CASP framework, all three studies formulated a clearly focused question and case-control study design was the most appropriate methodology to address it, since it would have been unethical to deliberately expose a population to a potentially harmful risk factor. In Greer et al.’s (2005) and McGuire et al.’s study (2004), the age range of the participants was similar and vast, increasing the comparability of the two studies and the applicability of their findings to the general population. In Ness et al.’s study (2011), no age range was specified for the study population, limiting the clarity of the formulated question. Furthermore, participants were generally older than in the other two studies, affecting the results.

In Ness et al.’s study (2011), cases were referred from hospital cancer registries, clinical practices or pathology databases within the western Pennsylvania region. In total, 859 cases were recruited, all diagnosed within the previous nine months. Controls were randomly selected by random digit dialing. Such selection method is a cost-effective way of covering a specific geographical area, by randomly generating telephone numbers. This method not only eliminates selection bias, but ensures total area coverage by including telephone numbers that are not listed in phone books. All 1779 controls were matched by age (five-year groups) and geographical location to the cases. In Greer et al.’s study (2005), 608 cases were recruited between 1994 and 1998 from hospitals in the Delaware Valley. Cases
were recruited following diagnosis with epithelial ovarian cancer, analysis for exclusion criteria and consent from the participants and consulting physicians. Controls (926) were enrolled after being selected either by random digit dialling and matched by race, age and geographical location, or through Health Care Financing Administration lists and matched by location. McGuire et al. recruited 417 cases by a rapid case ascertainment system. Such system allows quick identification of cancer patients within one month from diagnosis and includes pathology reports from the Greater Bay Area Cancer Registry for more detailed data that can be used for research purposes. Controls (568) were chosen at random via random digit dialing and matched by age, race or ethnicity and location. In all three studies, cases and controls were matched to potentially confounding variables, such as age and geographical location, increasing homogeneity of the participants. In Greer et al.’s (2005) and McGuire et al.’s study (2004), cases and controls were also matched by race, further reducing confounding variables. In this type of study design, the larger the control-to-case ratio, the higher the validity of the findings. By comparison, such ratio was largest in Ness et al.’s study (2011), therefore its findings are the most valid. The study also had the largest population (cases and controls combined), thus the most robust findings.

Participants in Ness et al.’s study (2011) were questioned in a standardised interview by trained interviewers at home about their reproductive, contraceptive, gynaecological and medical history as well as lifestyle factors. ‘Life’ calendars marked with important life-events were used to enhance recall of the participants. The type, frequency, duration and reason for use of oral contraceptives were all identified. Greer et al. (2005), used a structured questionnaire to identify the type, duration, reason for initiating and stopping oral contraceptive use. To enhance recall and thus, the validity of data collected, authors used life-events calendars marked with important lifetime events for each participant. Additionally, oral contraceptive users were presented with books containing photographs of oral contraceptives. Bias was further reduce by blinding participants and interviewers to the research question being addressed. McGuire et al.’s study (2004) used a structured interview and detailed questionnaire to ask about reproductive and medical history, alcohol and tobacco use as well as ever use and duration of oral contraceptives. Additionally, blood or buccal mouthwash samples were taken from cases for detection of BRCA1 gene mutations. Most participants were unaware of their germ-line status and its link to ovarian
cancer, therefore, some element of blinding was present. In all studies, temporal relation is correct, in that exposure preceded the outcome.

All three studies used standardised methods of collecting data, thus reducing subjectivity of the data collected and minimising bias. Ness et al. (2011) also used trained interviewers to conduct the interviews, increasing the quality of data collection. Life-events calendars were used by both Ness et al. (2011) and Greer et al. (2005) to improve recall, this not only enhanced the quality of the data, but also reduced recall bias. Greer et al. (2005) further reduced recall bias by using books containing pictures of oral contraceptives for better identification of the formulations used.

The three studies used the Chi-square test to obtain odds ratios (OR) and estimate the exposure’s effect strength, confirming heterogeneity. Ness et al. (2011) and Greer et al. (2005) used unconditional logistic regression to adjust for confounding factors, while McGuire et al. (2004) used conditional logistic regression. Unconditional logistic regression is used when cases are not matched to controls for the confounding factors, if the two are matched, then conditional logistic regression would be more appropriate. Different methods were used due to the fact that cases and controls were only matched for confounding variables in McGuire et al.’s study (2004) and matched for broad criteria only (e.g. age) in the other two.

The main confounding factors were accounted for in all three studies and data were adjusted accordingly. Common confounding variables included race, education, family history of cancer and parity. Following analysis of the studies using the CASP tool, it can be concluded that the results obtained by the authors were valid and reliable, with all three studies having a good design, method and data analysis. Despite this, the extent to which the findings of Ness et al. (2011) and Greer et al.’s study (2005) could be applied to the local population is limited, particularly due to the difference in lifestyle and cultural factors between the two populations.

Other limitations include the use of multiple contraceptive methods by participants in Ness et al.’s study (2011), which might have affected the reliability of the results. However, the author has acknowledged such limitation. The retrospective nature of data collection used
in all three studies may also have led to incorrect data being gathered as well as introduction of recall bias. Despite measures taken by some authors (such as life-events calendars and picture books), some element of of inaccuracy may still be present, affecting validity of the results. Such limitation is acknowledged by Greer et al., but not by the other authors. Greer et al.’s study (2005) had a considerable drop-out rate, where 30% of cases and 40% of the controls dropped out. The author acknowledged this limitation and stated that attrition bias was unlikely since non-responsiveness was unrelated to the participants’ experience of oral contraceptives. McGuire et al. (2004) did not test controls for their germ-line status, due to financial constraints. This resulted in inaccurate comparison between the two statuses as BRCA1 gene mutation carriers may have been included but not acknowledged, thus affecting the homogeneity of the participants. Furthermore, statistical significance of the results was limited as the number of gene mutation carrier cases was small, as acknowledged by the author, thus limiting robustness of the findings.

### 3.4 Ethical Issues

Although the research question and literature reviewed examine the protective effect of oral contraceptives on ovarian cancer, such secondary use of oral contraceptives should be employed with caution. As healthcare professionals, we are duty-bound to be benevolent and non-maleficent to our clients, one must therefore ensure that the beneficial effects of oral contraceptives outweigh the harmful or less beneficial ones, prior to encouraging oral contraceptive use. When promoting oral contraceptive use for its protective effect against ovarian cancer to those having an increased risk, such as BRCA1 or BRCA2 gene mutation carriers, consideration should be given to the primary effect of oral contraceptives, i.e. contraception. In the majority of the studies, the age range of participants included those in their early stages of adulthood, when individuals are trying to establish a family of their own and childbearing is a priority. Such individuals may therefore not be ready to compromise their reproductive ability, and therefore their goals, so other alternatives may be required.
Although no references to gaining permission from ethical committee boards are made in any of the studies, publication and inclusion in journals implies that such permission was in fact gained. Only three studies included gaining informed consent from their participants (Greer et al., Ness et al. and McGuire et al.), omission of such detail may however have occurred due to the word limit many articles have when getting published. Losing participants to follow-up in itself implies that participants had a right to refuse and a right to withdraw from the research study.

The sensitive nature of the research question means that individuals invited to participate in such studies may refrain from doing so for several reasons. In high-risk groups, such as gene-mutation carriers, which is usually hereditary, the individual may be grieving for a loved one lost to ovarian cancer, therefore participating in such study would not appeal to them. Furthermore, individuals may not wish to disclose information on their contraceptive use, which might be a taboo subject for some, and therefore opt out of the study.

Finally, one needs to consider the generalisability of the findings. Factors such as lifestyle, ethnicity, cancer disposition and other genetic factors are all important variables and play a role in the extent to which the findings can be applied to another population and should therefore be considered prior to doing so. In the next chapter, a discussion of the findings of the studies chosen for this critical appraisal following evaluation using the CASP tools is presented and an answer to the PICO question is given, based on the same literature findings.
Chapter 4:
Discussion
4.1 Introduction

In this chapter the findings of the papers chosen for this study are discussed in respect of the PICO question. Additionally, the local health scenario is also considered in the discussion of the findings.

In this study the effect of oral contraceptives on the risk of ovarian cancer in premenopausal as well as postmenopausal women was explored. The findings are discussed according to the methodology utilised in each paper in the order ranked in the hierarchy of evidence presented in the previous chapter.
4.2 Discussion of the findings

4.2.1 Discussion of the findings in systematic reviews with meta-analysis

**Table No. 10: Findings in Systematic Reviews**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Sample</th>
<th>Comparison</th>
<th>Findings</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beral et al. (2008)</td>
<td>Systematic review</td>
<td>110,000 (45 studies)</td>
<td>Duration of the protective effect of oral contraceptives against ovarian cancer in older adult females diagnosed with malignant non-epithelial ovarian cancer vs healthy females</td>
<td>-Overall relative risk for ever-users <em>versus</em> never-users RR 0.73 -20% reduction in risk per five years of use -No difference in risk reduction for age at first and last use</td>
<td>-P &lt;0.001 -P&lt;0.001</td>
</tr>
<tr>
<td>Iodice et al. (2010)</td>
<td>Systematic review</td>
<td>13,627 (18 studies)</td>
<td>Protective effect of oral contraceptives against ovarian and breast cancer in BRCA1/2 carriers vs non-carriers</td>
<td>-50% reduction in ovarian cancer risk in ever-users <em>versus</em> never-users -20% reduction in risk per five years of use -No differences in risk reduction between BRCA1 carriers and BRCA2 carriers</td>
<td>-P&lt;0.01 -P&lt;0.88</td>
</tr>
</tbody>
</table>
Two of the papers that were chosen were systematic reviews. As illustrated in Table 10, Beral et al. (2008) examined the duration of the protective effect against ovarian cancer of oral contraceptives by comparing older adult females diagnosed with malignant epithelial and non-epithelial ovarian cancer with healthy females. The mean age of all the cases combined was fifty-six years and the median year of diagnosis was 1993. In the other systematic review, Iodice et al. (2010), analysed for differences in the protective effect of oral contraceptives against ovarian and breast cancer between BRCA1/2 gene mutation carriers and non-carriers, since gene mutation carriers have an increased risk of being diagnosed with breast and ovarian cancer. For the purpose of this study, only the findings related to ovarian cancer will be analysed in depth. The overall findings of the studies were included in both reviews, as well as the findings of the individual studies in the form of forest plots and RR. Forest plots are graphic representations of the relative quantitative strength of an effect (such as a treatment), in a study comparing multiple effects. Relative risks, on the other hand, are ratios of the probability of the occurrence of an event by comparing the risk between two exposures. A RR of one means that there is an equal risk between the two exposures, while a RR of less than one indicates that the outcome is less likely to occur in the cases than in the control group, and the opposite, should the RR be larger than one.

In both studies, a statistically significant reduction in ovarian cancer risk for ever-users versus never-users was observed. Iodice et al. (2010) observed a larger risk reduction in their population of BRCA1/2 gene mutation carriers than was observed in the general population by Beral et al., (2010) (RR 0.50 versus RR0.73 respectively) implying that oral contraceptives may perhaps be advised as a prophylactic measure to those carrying the gene mutation. Additionally, an overall highly significant reduction of 20% for each five years of oral contraceptive use was observed in both studies indicating that the longer the duration of oral contraceptive use, the more significant the reduction in risk. Beral et al. also analysed the duration of such protective effect. It was observed that for current users and those who had ceased using oral contraceptives in the past ten years, a 29% reduction in risk was observed, while in those who had stopped use for ten to nineteen years, this reduction amounted to 19%, as opposed to the 15% reduction in risk in twenty to twenty-nine years since last oral contraceptive use. This attenuation in the protective effect
suggests that oral contraceptives may be indicated later in life, when ovarian cancer is most prevalent, not for their contraceptive effect, but as a prophylactic measure against ovarian cancer, especially to those with an increased risk of diagnosis.

Beral et al. also analysed for any effect on ovarian cancer risk by the age at first or last oral contraceptive use, but none was evident. This implies that oral contraceptives may be used later on in life for their protective effect alone, rather than for contraception. Iodice et al., on the other hand, analysed for any differences in risk reduction between carriers of the BRCA1 gene and the BRCA2 gene, however none were observed. Finally, Beral et al. concluded that risk reduction was uniform for all but one ovarian tumour types, since the reduction in risk was significantly smaller for mucinous tumours (4% risk reduction per five years of use). This means that the protective effect of oral contraceptives against ovarian cancer should be evaluated with caution, as it is not equal for all tumour types. Literature shows that mucinous ovarian tumours are moderately prevalent when compared to other histological sub-types. The Irish National Cancer Registry (2012), for example, has estimated that 11% of diagnosed invasive ovarian cancers are mucinous in origin, the prevalence increases to 50% of all borderline ovarian tumours. No local statistics on the prevalence of ovarian cancer by histological subtype could be retrieved. This raises the need for studies specifically evaluating the differences in protective effect of oral contraceptives by histological origin of ovarian tumours, to further analyse this discrepancy in risk reduction, especially since the authors gave no explanation for such a significant difference.

In both reviews, minor discrepancies can be observed between the findings of the different studies included, however these are not statistically significant and no conflicting results were obtained from the studies. The findings are summarized in Table 10. The large population included in both reviews and that fact that participants varied in their ethnicity, coming from various continents, means that their findings are highly significant and robust. However, all countries were high-income, therefore the findings may not apply to middle-income and low-income countries due to a lesser availability and usage of oral contraceptives (Beral et al., 2008). Iodice et al.’s population consisted mainly of BRCA1/2 gene mutation carriers, an inheritable mutation and as stated by the authors, most
participants were related. Therefore, this could have affected the results as the participants were not representative of the general affected population. However the authors noted that the findings may still be generalised to the same population as no significant differences exist between the two populations. Additionally, even though no difference in risk reduction was observed between the two gene mutation types, the authors failed to present separate data for the individual gene mutation types. Furthermore, the authors did not present data for different histological types of ovarian cancer, therefore such findings are applicable to ovarian cancer in general, and not to specific histological subtypes. In Beral et al.’s study (2008), the majority of oral contraceptive use among the participants had occurred in the 1970s. At that time, preparations with higher doses of oestrogen were available, therefore such findings may not be applicable to those currently using oral contraceptives, due to lower doses of oestrogen present in current preparations, and further research in this area is required.

These reviews conclude that oral contraceptive users are at a reduced risk of being diagnosed with ovarian cancer, that such protective effect is strengthened with increased duration of use and persists for decades after stopping use. Such effect is stronger for BRCA1/2 gene mutation carriers, but much weaker in mucinous tumours than in all other histological types of ovarian cancer, raising the need for further literature. Iodice et al. concluded no statistically significant increase in breast cancer risk associated with recent formulations of oral contraceptives in their population. This means that with additional literature evaluating the risk-to-benefit ratio, oral contraceptives may be considered as a prophylactic measure against ovarian cancer in gene mutation carriers. This highly contradicts popular belief that oral contraceptives should be avoided by such individuals.
### 4.2.2 Discussion of the findings in cohort studies

**Table No. 11: Findings in cohort studies**

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>Sample</th>
<th>Comparison</th>
<th>Findings</th>
<th>P-value</th>
</tr>
</thead>
</table>
| Vessey and Painter (2006) | Cohort study | 17,032 | Oral contraceptives and incidence of cancer, including ovarian cancer in 25-39 year old females recruited from family planning clinics in the UK, followed for thirty-six years. | -Overall rate ratio for ever-users versus never-users Rr 0.50  
-Rr 0.30 ovarian cancer risk for 4 and ≥ 9 years of use  
-Rr 0.60 20 years after stopping use | -P<0.001  
-P<0.05  
-P<0.05 |
| Hannaford et al. (2007) | Cohort study | 45,950 | Cancer risk among oral contraceptive users (mean age 29 years), recruited from participating GP in the UK, followed for thirty-six years. | -Overall RR for ovarian cancer risk in ever-users versus never-users is RR0.54  
-Risk inversely proportional to duration of use  
-Protective effect evident 20 years after stopping use | -Not included  
-Not included  
-Not included |
| Tworoger et al. (2007) | Cohort study | 107,900 | Duration of the protective effect of oral contraceptives against ovarian cancer and effects of other contraceptives in 30-55 year old American registered nurses followed for twenty-eight years through questionnaires. | -Reduction in risk in ever-users versus never-users  
-Risk inversely proportional to duration of use  
-Risk proportional to time since stopping use  
-RR 0.88 20 years after stopping use | -Not included  
-P<0.02  
-P<0.65  
-P<0.57 |
As shown in Table 11, Vessey and Painter (2006) observed the relationship between oral contraceptives and the incidence of ovarian, breast, cervical and endometrial cancer in over 17,000 females, while Hannaford et al. (2007) analysed the risk of cancer in 46,000 females, half of which were oral contraceptive users. Both studies followed their participants for thirty-six years. Two data sets were compiled for Hannaford et al.’s (2007) study. Data from the GP data set lost most of its statistical significance due to a lesser degree of accuracy when compared to the main data set. This occurred since data for the GP data set were compiled up until 1996, whilst that for the main data set continued until 2004, therefore consideration is given to the findings of the main data set alone. Tworoeger et al. (2007) analysed the association between oral contraceptive use and the duration of the protective effect against ovarian cancer, as well as the effect of other contraceptive methods and infertility on the same cancer. Their population consisted of over 100,000 female nurses who were followed for twenty-eight years. Whilst the other two studies presented their findings as RR, Vessey and Painter (2006) presented theirs as rate ratios (Rr). A Rr compares the incidence rates of an outcome based on person-years and although similar to RR, is preferred when measuring for causality of a disease, as in the case of this cohort study. However, both methods are appropriate to the study design used here.

Ovarian cancer risk was significantly reduced for ever-users versus never-users in all three studies. Such risk was inversely proportional to duration of oral contraceptive use, so that a longer duration of use meant a smaller risk. In Vessey and Painter’s study (2006) for those using oral contraceptives for four to nine years and for nine years or more, a Rr of 0.30 could be observed for ovarian cancer. However, for those using oral contraceptives for less than four years, no difference in ovarian cancer risk could be observed, suggesting that the protective effect may require a minimum duration of use for it to be observed. This contradicts the finding of another study that suggests that a protective effect is provided with a duration of oral contraceptive use as short as six months (Greer et al., 2005). This may have occurred due to an incomplete follow-up for the group of participants using oral contraceptives for less than four years, as it ceased at age forty-five. Further research is therefore necessary for a clear conclusion to be made. Hannaford et al.’s participants who had used oral contraceptives for up to four years, had a RR of 0.42, which was increased to RR 0.57 and 0.38 for five to eight years, and more than eight years of use, respectively. In
Tworoger et al.’s study (2007) a RR of 0.75 for five to ten years of use, and RR 0.62 for more than ten years of oral contraceptive use was observed. The duration of the protective effect was also analysed by assessing the risk according to time since last oral contraceptive use. Such an effect is highly persistent, as it could still be observed after twenty years of ceasing use in all three study populations.

Additionally, Tworoger et al. (2007) also analysed reduction in risk according to duration of use and time since last use. A RR of 0.58 could be observed for those who had used oral contraceptives for more than five years and had stopped use less than twenty years previously. The reduction in risk was lower with a shorter duration of use and a longer time since use cessation. Similar results were obtained for all histological types of ovarian tumours, with the protective effect being strongest for endometrioid tumours. Furthermore, neither age at first, nor last oral contraceptive use had any effect on ovarian cancer risk in their participants.

The findings in all three studies were consistent with each other and are summarized in Table 11. Hannaford et al. (2007) also observed a 12% reduction (RR 0.88) in the risk of any cancer and a a 29% reduction (RR 0.79) in the risk of the main gynaecological cancers combined. Small increases in the risk of certain types of cancer, such as that of the lungs and the cervix were observed, however these were not statistically significant. These findings further strengthen the beneficial effects of oral contraceptives against cancer. The findings of this study are more robust than those of Vessey and Painter (2006), since although both studies have an equal duration of follow-up, Hannaford et al. (2007) used a much larger cohort. However, applicability of the findings to the general population may be limited in both studies. Vessey and Painter’s participants attended family planning clinics and according to the authors, were generally more health conscious and pertained to a higher social class. Hannaford et al., on the other hand, excluded participants suffering from chronic illnesses, which are becoming increasingly common in high-income countries (WHO, 2005), therefore further literature is necessary to evaluate the effect of oral contraceptives on ovarian cancer in those suffering from chronic conditions, especially since such contraceptive method is contraindicated in certain chronic illnesses.
Although the findings by Tworoger et al. (2007) were consistent with those of the other two studies, the risk reduction was much lower. Incidence of smoking, a risk factor for cancer, is higher amongst nurses than in the general population, (Rowe and Clark, as cited in Berkelmans et al., 2010) as is a higher BMI (Kim et al., 2013). However, the fact that the population consisted of nurses, should not have affected the findings, as Hannaford et al. (2007) concluded that oral contraceptives provide a protective effect regardless of other risk factors being present. Participants of this study had an older mean age than in the other two studies, therefore time since last oral contraceptive use was likely to be longer and the risk reduction weaker. In fact, when the authors tried excluding the last four years of follow-up from their analysis, the risk reduction for more than ten years of oral contraceptive use was increased to 52% as opposed to the previous 38% risk reduction. This is more comparable to the findings in Vessey and Painter’s (2006) and Hannaford et al.’s (2007) studies who observed a 70% and a 62% risk reduction in participants using oral contraceptives for more than eight years respectively.
4.2.3 Discussion of the findings in case-control studies

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study design</th>
<th>Sample</th>
<th>Comparison</th>
<th>Findings</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ness et al. (2011)</td>
<td>Case-control study</td>
<td>859 (cases) 1,779 (controls) matched by age and geographical location</td>
<td>Effects of different contraceptives on ovarian cancer in ≥25 year old females diagnosed with epithelial ovarian, peritoneal or Fallopian tube cancer (cases) and healthy females (controls)</td>
<td>-Reduction in risk in ever-users versus never-users of oral contraceptives -Stronger reduction when using for contraception -No risk difference with gravidity -Risk inversely proportional to duration of use</td>
<td>-Not included -Not included -Not included -Not included</td>
</tr>
<tr>
<td>Greer et al. (2005)</td>
<td>Case-control study</td>
<td>608 (cases) 926 (controls) matched by age and geographical location</td>
<td>Protective effect of short-term oral contraceptive use against ovarian cancer in 20-69 year old females with confirmed epithelial ovarian cancer (cases) and healthy females (controls)</td>
<td>-OR0.73 for &lt;6 months use (single episode) versus never-use -OR0.75 for &lt;6 months use (multiple episodes versus never-use -Significant protective effect in short-term use ceased due to side-effects -Protective effect in ≥6 months of use, regardless of reason for stopping use</td>
<td>-Not included -Not included -P&lt;0.05 -P&lt;0.05</td>
</tr>
<tr>
<td>McGuire et al. (2004)</td>
<td>Case-control study</td>
<td>417 (cases) 568 (controls) matched by age and race/ethnicity</td>
<td>Reproductive and contraceptive history and ovarian cancer risk in 20-64 year old BRCA1 carriers/non-carriers diagnosed with invasive epithelial ovarian cancer (cases) and healthy non-carriers (controls)</td>
<td>-13% risk reduction per year of use in carriers -6% reduction in risk per year of use in non-carriers -Risk inversely proportional to duration of use -Risk lower in carrier-users than in non-carrier users</td>
<td>-P&lt;0.01 -P&lt;0.001 -Not included -Not included</td>
</tr>
</tbody>
</table>
Ness et al. (2011) studied the effects of different contraceptive methods, including oral contraceptives, on ovarian cancer in 859 cases and 1779 controls. Oral contraceptive use was further divided into reasons for use, including contraception, non-contraception, such as dysmenorrhea, hirsutism or acne, and both. A distinction between no use of artificial contraceptives in general and no use of oral contraceptives was also made. Greer et al. (2005) examined whether short-term use of oral contraceptives provides a protective effect against ovarian cancer amongst 608 cases of incident epithelial ovarian cancer and 926 controls. Short-term oral contraceptive use was subdivided into continuous use, i.e. one short episode, or intermittent use, i.e. multiple short-term episodes. McGuire et al. (2004) studied the relation of the reproductive and contraceptive history to ovarian cancer risk in a population of 417 BRCA1 carriers and non-carriers diagnosed with invasive epithelial ovarian cancer as cases and 568 healthy non-carriers as their study controls. In all three studies, results were presented as OR and are summarized in Table 12. OR are used to quantify how strongly the presence or absence of an outcome is in relation to the presence or absence of an exposure within a defined population. If OR is greater than one, then the outcome is associated with the exposure, if the OR is less than one, then the exposure may decrease the occurrence of the outcome.

In Ness et al.’s study (2011), an OR of 0.66 for ever-users of oral contraceptives for contraception versus never-users of oral contraceptives was observed, while such risk was slightly increased to OR 0.73 for ever-users for non-contraceptive reasons versus never-users and decreased to OR 0.58 for ever-users for both reasons versus never-users. The risk of ovarian cancer in ever-users of oral contraceptives versus users of no artificial contraception was also analysed. Ever-users for contraceptive reasons had an OR of 0.45 when compared to no use of contraceptives, while ever-users for non-contraceptive reasons had an OR of 0.41 for ovarian cancer. Risk in ever-users versus never-users according to gravidity was analysed, with a reduction being observed in nearly all groups, however no clear trend was established. Similarly, Greer et al. (2005) observed that users for one episode of less than six months had an OR of 0.73 when compared to never-users, and a similar OR (0.75) was observed when oral contraceptives were used during multiple episodes amounting to less than six months.
The effect of duration of oral contraceptive use on ovarian cancer risk was assessed with a decrease in risk being observed with an increasing duration of use in all three studies. Ness et al. (2011) concluded that with ten or more years of use, an OR of 0.52, 0.53 and 0.40 could be observed when oral contraceptives were used for contraception, non-contraception and both uses, respectively. In Greer et al.’s study (2005) the most significant reduction in risk could be observed when oral contraceptive use lasted thirteen months or more, whether with continuous or intermittent use (OR 0.63 and 0.56 respectively). No clear trend could be established across duration of short-term episodes, whether continuous or intermittent. McGuire et al. (2004) observed that ovarian cancer risk was reduced by 13% per year of oral contraceptive use in BRCA1 carriers and by 6% per year of use in non-carriers. An OR for ovarian cancer of 0.54 in carriers and 0.55 in non-carriers was observed in those using oral contraceptives for one year or more, when compared to those using them for less than a year. A more significant reduction was observed in carriers and non-carriers with OR of 0.25 and 0.43 respectively when using oral contraceptives for more than seven years compared to those using them for less than one year.

Greer et al. (2005) also analysed the ovarian cancer risk of those who used oral contraceptives for one episode according to reason for ceasing use. Reasons for stopping use included unpleasant side-effects or other reasons that did not include side-effects. Those who used oral contraceptives for less than six months and terminated due to side-effects had a significant reduction in ovarian cancer risk of OR 0.59, however those who stopped for other reasons had no significant reduction in risk. Similar results were obtained when the episode lasted more than six months, with slightly lower OR. A reason for such findings may be that oral contraceptives have a greater bioactivity in these women. Such increase in bioactivity may occur due to altered liver enzyme activity, which maintains hormones at lower levels in the bloodstream, but for a longer period. This means that ovulation and gonadotropin levels are suppressed more effectively, leading to a greater reduction in ovarian cancer risk. However, it also means that side-effects are experienced to a greater extent in these women.

To test this hypothesis, authors categorized reason for stopping use according to the type of oral contraceptive being used (whether low-dose COC, high-dose COC or POP). No
significant difference was observed, therefore strengthening the hypothesis that increased side-effects are associated with altered liver enzyme activity, and not oral contraceptive preparation. Although individuals with altered liver enzyme activity benefit from a stronger protective effect, consideration must be given to the nature and severity of the experienced side-effects, especially since the authors did not elaborate on the subject. Oral contraceptive use may negatively affect the health and quality of life of such individuals, rendering use inappropriate.

These studies measured exposures and outcomes not previously included in the other studies, therefore making their findings highly valuable. Ness et al. (2011) concluded that risk reduction for ovarian cancer is stronger when oral contraceptives are used for contraceptive methods, rather than for other reasons, however the authors gave no clear explanation for this finding. Greer et al.’s study (2005) is the largest available that has evaluated the effects of such short-term use of oral contraceptives. The findings conclude that short-term oral contraceptive use also provides a significant protective effect against ovarian cancer, regardless of whether used in single or multiple episodes. However, such protective effect is exclusive to use being ceased due to side-effects, which may be due to the reason discussed previously. When oral contraceptives are used for longer than six months, the protective effect is observed regardless of the reason for terminating use. This contradicts the findings of Vessey and Painter’s study (2006), who observed no difference in risk for less than four years of oral contraceptive use. However, this group of participants had an incomplete follow-up which may have influenced the results. This raises the need for more studies analysing the minimum duration of oral contraceptive use necessary for the protective effect to be evident.

The findings by McGuire et al. (2004) are consistent with those presented in Iodice et al.’s study (2010) who observed the same protective effects in BRCA1 and BRCA2 carriers as in the general population. Furthermore, as in Iodice et al.’s study (2010), such protective effects are stronger in the gene mutation carriers than in the general population. The larger reduction in risk associated with longer use of oral contraceptives is also consistent with all other findings in studies of the general population. This study has the smallest population of the three studies included in this literature review, this may be due to the focus in
population included. Such limitation may affect the robustness of the findings, however it is to be noted that these findings are consistent with those in Iodice et al’s study. (2010), who had a much larger population of over 13,000 individuals with gene mutation carriers as cases.

The findings are consistent with all other studies analysed before, despite having different study designs and data analysis methods. Since the protective effect of oral contraceptives against ovarian cancer is independent to all statistical variables, and prevails across varying methodologies, it can be concluded that these findings are robust.
## 4.3 Conclusion

### 4.3.1 Answering the PICO question

**Table No. 13: Overall findings**

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>Population</th>
<th>Risk (ever-users vs never-users)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beral <em>et al.</em> (2008)</td>
<td>Systematic review with meta-analysis</td>
<td>Older adult females diagnosed with malignant non-/epithelial ovarian cancer (cases), healthy females (controls)</td>
<td>RR 0.73 (p &lt;0.001)</td>
</tr>
<tr>
<td>Iodice <em>et al.</em> (2010)</td>
<td>Systematic review with meta-analysis</td>
<td>Adult females having a BRCA1/BRCA2 gene mutation (cases), BRCA1/BRCA2 non-carriers (controls)</td>
<td>50% risk reduction (p&lt;0.01)</td>
</tr>
<tr>
<td>Vessey and Painter (2006)</td>
<td>Cohort study</td>
<td>25-39 year old married British females</td>
<td>Rr 0.50 (p&lt;0.01)</td>
</tr>
<tr>
<td>Hannaford <em>et al.</em> (2007)</td>
<td>Cohort study</td>
<td>Married British females (mean age 29 years), mainly Caucasian</td>
<td>RR 0.54 (p-value not included)</td>
</tr>
<tr>
<td>Tworoger <em>et al.</em> (2007)</td>
<td>Cohort study</td>
<td>30-55 year old married American registered nurses</td>
<td>Reduction in risk, no value given (p-value not given)</td>
</tr>
<tr>
<td>Ness <em>et al.</em> (2011)</td>
<td>Case-control study</td>
<td>≥25 year old female adults diagnosed with primary epithelial ovarian, peritoneal, Fallopian tube cancer (cases) and healthy individual (controls)</td>
<td>Reduction in risk, no value given (p-value not given)</td>
</tr>
<tr>
<td>Greer <em>et al.</em> (2005)</td>
<td>Case-control study</td>
<td>20-69 year old females with confirmed epithelial ovarian cancer (cases) and healthy individuals (controls)</td>
<td>-OR0.73 for &lt;6 months use (single episode) (p-value not given) -OR0.75 for &lt;6 months use (multiple episodes (p-value not given)</td>
</tr>
<tr>
<td>McGuire <em>et al.</em> (2004)</td>
<td>Case-control study</td>
<td>20-64 year old females diagnosed with invasive epithelial ovarian cancer: BRCA1 carriers/non-carriers (cases) and healthy non-carriers (controls)</td>
<td>Not measured (no p-value given)</td>
</tr>
</tbody>
</table>
The findings of all the studies presented here are summarised in Table 13 above. Nearly all findings are inclined towards the same direction. However, conflicting evidence was found for the minimum duration of oral contraceptive use necessary for the protective effect to be evident between Vessey and Painter (2006) and Greer \textit{et al.} (2005). Such findings conclude that oral contraceptives reduce the risk of ovarian cancer. This reduction in risk is present in ever-users of oral contraceptives when compared to never-users. Furthermore, the risk continues to be reduced with an increased duration of oral contraceptive use and persists for up to twenty years after stopping oral contraceptives. Such reduction is not only present in the general population, but also in those carrying the BRCA1 and BRCA2 gene mutations, who are generally more prone to being diagnosed with ovarian cancer. No literature comparing the extent to which ovarian cancer risk is reduced in pre-menopause \textit{versus} post-menopause could be identified, however, most studies had a wide age range in their population, which included women in both stages of life. Such a study would be appropriate as it would give an indication to the best time that oral contraceptives should be used for ovarian cancer prevention, especially since such cancer is mostly prevalent in women aged fifty-five years and older, when oral contraceptives are not used for contraception due to menopause.

Such a benefit must however be analysed with caution, as due consideration should be given to the adverse effects of oral contraceptive use. Such adverse effects are well documented in the literature, have varying degrees of severity and include tenderness of the breast, nausea and an increased risk of venous and arterial thrombotic events (Guida \textit{et al.}, 2010), mood changes, facial pigmentation and decreased menstrual flow, (Shakerinejad \textit{et al.}, 2013) as well as headaches and decreased libido (Küçük \textit{et al.}, 2012). This means that prior to advising oral contraceptives as a prophylaxis against ovarian cancer, the health status and risk factors of the individual client should be analysed. This is because risk factors for severe side-effects, such as thrombotic events, may rule out the possibility of using oral contraceptives at all.

Another reason for resistance to using oral contraceptives in practicing Catholic women may be due to the negative religious connotation associated with using artificial methods of contraception, especially in unmarried women. Using oral contraceptives prior to marriage
may imply that the female is sexually active, something that is unacceptable by the Catholic Church, which is the main religion in Malta. Additionally, making use of oral contraceptives after marriage is also considered immoral. This is due to the fact that by doing so, the possibility of procreation is eliminated and sexual intercourse should be procreative in nature, according to Catholicism (Pope Paul VI, 1968). Although the Church has not given its opinion on using oral contraceptives for therapeutic reasons, one must take into account the literature findings and the fact that an estimated 200,000 incident cases and 100,000 deaths from ovarian cancer have been prevented since the late 1950s (Beral et al., 2008) and this is likely to increase with increased oral contraceptive use. This means that oral contraceptives help protect human life, a fundamental moral of Catholicism. Such a benefit of oral contraceptives must be carefully weighed against the contraceptive effect they exert and the associated religious standards, especially in those at high risk of being diagnosed with ovarian cancer. The client’s health status and priorities must therefore be analysed in order to evaluate the risk-to-benefit ratio and help make an informed decision as to whether oral contraceptives are the best method of prophylaxis against ovarian cancer.

Despite providing such a protection against ovarian cancer, oral contraceptives are still perceived as being carcinogens by the general population. This has been contradicted by Hannaford et al. (2007) who observed a 12% reduction in the general risk of cancer in their population of 45,950 British females. Such misconception highlights the need for better education being provided by healthcare professionals, such as nurses, in order to increase the awareness of clients. According to the latest publication by the Malta National Cancer Registry (Department of Health Information, 2000), ovarian cancer ranked as the fourth most common site of cancer diagnosed between 1998 and 2000. During the same period, ninety-nine new cases were diagnosed and fifty-five females died from ovarian cancer, amounting to 6% of all female cancer deaths. Most diagnosed cases were aged thirty to fifty-nine years (thirty-nine cases) and between sixty and seventy-four years (forty-four cases). Oral contraceptives have helped reduce the number of ovarian cancer cases and deaths since their introduction, and this number is expected to increase with the ageing of past users and a projected increase in popularity of use, especially in middle-income and low-income countries (Beral et al., 2008).
4.3.2 Gaps in the literature

Ample literature is available on this topic, however gaps in the literature are still evident. Oral contraceptives have been going through continuous changes in their preparation since their creation in the late 1950s, however the most drastic changes have occurred during the 1980s, at which time the doses of oestrogen used were halved (Ness et al. 2000 as cited in Beral et al. 2008). Most studies that are available have a long follow-up and have recruited their cohorts as early as 1968, at which time high-dose oral contraceptives were still being used. For this reason, a need for more recent studies exists in order to evaluate whether such protective effects are provided by the lower-dose preparations of oral contraceptives used today.

Another literature gap exists when evaluating the benefits of oral contraceptives and their adverse effects. Despite providing a protective effect against ovarian cancer, and other types of cancer clearly demonstrated in literature, a realistic evaluation is necessary to ensure that the benefits outweigh the risks, as only through this evaluation can oral contraceptives start being indicated for their cancer-preventing properties. Furthermore, bigger efforts are necessary to educate the public on the true harms and benefits that such pills provide and realistically promote oral contraceptive use. In the next chapter, interventions that may be used to accomplish this are discussed in more detail.
Chapter 5:
Recommendation and Dissemination of Findings
5.1 Introduction

The aim of this literature review was to analyse whether oral contraceptive use decreases the risk of ovarian cancer in females that are in the pre-menopausal and post-menopausal stages of their life. In this penultimate chapter, suggestions and recommendations for research and improvement of practice will be put forth, so that the findings of this study may be appropriately disseminated and utilised for practice.

5.2 Recommendations

5.2.1 Recommendations for education

Educating potential clients should start early on, preferably in the early teens, to ensure that the misconceptions and taboo that surrounds oral contraceptive use, especially within the local context, are eradicated and those considering using them, or are at high risk of being diagnosed with ovarian cancer, are not discouraged by any perceived adverse effects. Adequate, evidence-based client education may be achieved through seminars and talks held in secondary schools by appropriate healthcare professionals that are equipped with the latest literature findings and trained in health promotion.

Education may also be taken a step further by introducing the topic as part of the Personal Social and Career Development subject, which is taught in all secondary schools and whose aim is to educate students in non-academic areas including those of personal and social skills, and career advice. Teachers of the subject may be given a seminar to help introduce them to the topic and equip them with current evidence.

Providing written material would also be effective in educating the public. This may be done through leaflets and posters that may be handed out at pharmacies, health centres, gynaecologist and GP clinics as well as in hospital, in the Gynaecology ward and outpatient department. Through graphic representations, it is ensured that the findings are communicated and understood by the public.
Health care professionals should also be educated about the benefits of oral contraceptives, especially those involved in the field. Questionnaires may first be distributed among them to obtain an understanding of their current level of knowledge. Seminars may then be held for all healthcare professionals involved, such as gynaecologists, GP and nurses and doctors working in the Gynaecology ward and outpatient department within the hospital. During these seminars, valid literature may be analysed and its findings explained and disseminated. Additionally, it would also be appropriate to educate these healthcare professionals on the major public misconceptions of the effects of oral contraceptives and reasons for not using them, even when required. Through such education, healthcare professionals will be provided with evidence and alternatives to promote oral contraceptive use.

5.2.2 Recommendations for research

It is evident that there is a lack of research on the subject within the local setting, since no local studies could be retrieved during the research process. Doctors and nurses specialised in the field may be encouraged and given incentives to carry out research to be able to obtain a clearer understanding of current practice and usage patterns in the local population. This is not being done currently as evidenced by the lack of research. It would also be appropriate to look more deeply into the reasons why people refrain from using oral contraceptives and the public perception of such method of contraception. This would help tailor client education as well as promotion campaigns to ensure optimal effectiveness.

Additionally, more research is required on an international level to help close literature gaps. Such research may include younger participants who have been using oral contraceptives more recently, thus containing lower doses of oestrogen, rather than those used in the 1960s and are no longer available, as is the case with the largest, most cited studies currently available. This is necessary as oestrogen doses found in oral contraceptives in the 1960s were double that found in the 1980s, and doses have been further decreased ever since. Through this research, literature that is more reliable would be made available and a deeper understanding of the effects of current preparations of oral contraceptives.
contraceptives may be gained. This would help healthcare professionals form an informed professional opinion on the subject, thus educating and helping their clients weigh risks and benefits more realistically.

Due to the conflicting evidence found in Vessey and Painter’s (2006) and Greer et al.’s (2005) studies, further research is required to determine the minimum duration of oral contraceptive use necessary for the protective effect to be manifested. Another area that may be appropriate for research would be an evaluation of the risk-to-benefit ratio actually provided by oral contraceptives. Such research would provide a realistic analysis that would help conclude whether it is feasible to use oral contraceptives as a prophylactic method against ovarian cancer, especially by those at risk, such as those with a strong family history, or a BRCA1/2 gene mutation.

5.2.3 Recommendations for practice

Since no local literature is available, current practice methods are not documented, however oral contraceptive use in Malta is still relatively low (15.6%) (Savona-Ventura, 2012). This may be increased through further research and education. Educating healthcare professionals should be the first step, so that client education can then be made better, thus increasing public awareness of the subject.

Those with a strong family history of ovarian cancer may be screened early on through DNA screening. Those with a high risk may then be examined for the presence of any contraindications to using oral contraceptives and if none are found, they may be offered prophylactic use of oral contraceptives following detailed education and evaluation of their priorities, benefits and risks.
5.3 Dissemination of the findings

Not disseminating the findings of this literature review would mean that it is a futile exercise. These findings are beneficial to public health, as outlined by various authors, it is estimated that a large number of ovarian cancer cases have been prevented through oral contraceptive use. The number of prevented cases have been on a linear increase since the 1960s and are much larger in high-income countries (Beral et al. 2008, Hannaford et al. 2007, McGuire et al. 2004). This strengthens the need for adequate dissemination of evidence and education of the public, so that these numbers can be increased even further.

Seminars may be held for both public and healthcare professionals interested or involved in the field. Additionally, papers presenting a literature review of valid, current literature may also be published, directly targeting healthcare professionals, thus ensuring an improvement in client education and public perception. As aforementioned, leaflets and posters will also be beneficial in disseminating this information to the general public. Finally, public health campaigns targeting oral contraceptive use and its risks and benefits would also be appropriate, especially when considering the high mortality rate of ovarian cancer and the lack of public awareness of this type of cancer. The next chapter provides a summary of this study and concludes the literature review.
Chapter 6:

Conclusion
6.1 Methodology

Oral contraceptives have been created in the late 1950s and although literature suggests a reduction in certain cancers associated with the oral contraceptive use, public misconceptions still prevail. The aim of this review is to determine whether oral contraceptive use reduces the risk of ovarian cancer in women in their pre-menopausal and post-menopausal stage. A thorough search through the HyDi UoM search portal, which includes various databases such as the Cochrane Central Register of Controlled Trials and the CINAHL Plus with Full Text, has been performed. Additionally, manual searches in the UoM Health Sciences Library and reading through reference lists of valid studies has been carried out in an effort to retrieve the most valid studies related to the topic of interest that would help answer the PICO question. The search yielded two systematic reviews with meta-analysis, three cohort studies and three case-control studies which have been critically appraised and validated using the CASP critical appraisal tools. The findings suggest that oral contraceptives reduce the risk of ovarian cancer. This reduction in risk is present in ever-users of oral contraceptives when compared to never-users. Additionally, risk reduction is increased with an increased duration of use and persists for up to twenty years after stopping oral contraceptives. This reduction is not only present in the general population, but also in those carrying the BRCA1 and BRCA2 gene mutations, who are more prone to being diagnosed with ovarian cancer.

6.2 Recommendations

Further research is needed in this area, especially evaluating the risk-to-benefit ratio of oral contraceptives to enable informed decisions as to whether they can be used as a prophylactic measure for ovarian cancer. Most published studies evaluate formulations of oral contraceptives that were available in the 1960s, which contained much higher doses of oestrogen, therefore more recent studies are required for a more valid analysis of present formulations. No local literature was available for retrieval, thus respective health care professionals should be urged to carry out research to enable a clearer understanding of
current practice and usage patterns in the local population. Through this research, areas that require change could be identified and through the use of EBP, local practices would be ameliorated. Additionally, reasons for refraining from using oral contraceptives and public opinion on the subject could also be explored, allowing client education to be tailor-made.

### 6.3 Strengths and limitations

Although the literature search performed was vast and has yielded a large number of studies, it was difficult to extract studies that used a systematic review methodology, which is usually considered as being a highly reliable methodology to use, in fact only two systematic reviews were included in this analysis, which might have hindered the quality of the review. Furthermore, no literature comparing the extent to which ovarian cancer risk is reduced in pre-menopause versus post-menopause could be identified, thus limiting the depth of the analysis performed. Additionally, no related local literature could be retrieved, therefore the findings of these studies are based on foreign populations, limiting their applicability. This review is based on studies published in English that are available for free as full text, therefore some valid literature might have been missed. Strengths of this review include the thorough literature search that has been performed which included multiple sources that has enabled retrieval of a vast range of articles. All the studies that were included in the analysis are considered valid and reliable following thorough analysis and evaluation using the CASP critical appraisal tools. These studies have also included a large population, with the largest having included over 110,000 individuals, therefore making the findings robust. Additionally, all studies were published in internationally respected journals, such as the American Journal of Epidemiology and the British Journal of Cancer, making them reliable.
References


Appendix 1:
CASP Tools
Critical Appraisal Skills Programme (CASP)

making sense of evidence

10 questions to help you make sense of systematic review

How to use this appraisal tool

Three broad issues need to be considered when appraising the report of a systematic review:

• Are the results of the review valid? (Section A)
• What are the results? (Section B)
• Will the results help locally? (Section C)

The 10 questions on the following pages are designed to help you think about these issues systematically.

The first two questions are screening questions and can be answered quickly. If the answer to both is “yes”, it is worth proceeding with the remaining questions.

You are asked to record a “yes”, “no” or “can’t tell” to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.
Are the results of the review valid? (Section A)

Screening Questions

1. Did the review ask a clearly-focused question? □ Yes □ Can’t tell □ No
   Consider if the question is ‘focused’ in terms of:
   – the population studied
   – the intervention given
   – the outcomes considered

2. Did the authors look for the right type of papers? □ Yes □ Can’t tell □ No
   Consider if the included studies:
   – address the review’s question
   – have an appropriate study design

Is it worth continuing?

Detailed Questions

3. Did the reviewers try to identify all relevant studies? □ Yes □ Can’t tell □ No
   Consider:
   – which bibliographic databases were used
   – if there was follow-up from reference lists
   – if there was personal contact with experts
   – if the reviewers searched for unpublished studies
   – if the reviewers searched for non-English-language studies

4. Did the reviewers assess the quality of the included studies? □ Yes □ Can’t tell □ No
   Consider:
   – if the authors considered the rigour of the studies they have identified
   -lack of rigour may affect the studies’ results
5. If the results of the studies have been combined, was it reasonable to do so?

□ Yes □ Can’t tell □ No

Consider whether:
– the results of each study are clearly displayed
– the results were similar from study to study
(look for tests of heterogeneity)
– the reasons for any variations in results are discussed

What are the results? (Section B)

6. What are the overall results of the review?

Consider:
- if you are clear about the review’s ‘bottom line’ results
- what these are (numerically if appropriate)
- how were the results expressed (NNT, odds ratio etc.)

7. How precise are these results?

Consider:
– look at the confidence intervals, if given

Will the results help locally? (Section C)

8. Can the results be applied to the local population? □ Yes □ Can’t tell □ No

Consider whether:
– the population sample covered by the review could be different from your population in ways that would produce different results
– your local setting differs much from that of the review
– you can provide the same intervention in your setting
9. Were all important outcomes considered? □ Yes □ Can’t tell □ No

Consider whether:
– is there other information you would like to have seen

10. Are the benefits worth the harms and costs? □ Yes □ Can’t tell □ No

Consider:
– whether any benefit reported outweighs any harm and/or cost. If this information is not reported can it be filled in from elsewhere?
Critical Appraisal Skills Programme (CASP)

making sense of evidence

10 questions to help you make sense of cohort study

How to use this appraisal tool

How to use this appraisal tool

Three broad issues need to be considered when appraising the report of a cohort study:

• Are the results of the study valid? (Section A)
• What are the results? (Section B)
• Will the results help locally? (Section C)

The 12 questions on the following pages are designed to help you think about these issues systematically.

The first two questions are screening questions and can be answered quickly. If the answer to both is “yes”, it is worth proceeding with the remaining questions.

You are asked to record a “yes”, “no” or “can’t tell” to most of the questions. A number of italicised prompts are given after each question.

These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.
Are the results of the study valid? (Section A)

Screening Questions

1. Did the study address a clearly-focused issue? □ Yes □ Can’t tell □ No
 Consider if the question is ‘focused’ in terms of:
 – the population studied
 – the risk factors studied
 – the outcomes considered
 -is it clear whether the study tried to detect a beneficial or harmful effect?

2. Was the cohort recruited in an acceptable way? □ Yes □ Can’t tell □ No
 Look for selection bias which might compromise generalisability of the findings:
 – was the cohort representative of a defined population?
 – was there something special about the cohort?
 – was everybody included who should have been included?

Is it worth continuing?

Detailed Questions

3. Was the exposure accurately measured to minimise bias? □ Yes □ Can’t tell □ No
 Look for measurement or classification bias:
 – Did they use subjective or objective measurements?
 – Do the measurements truly reflect what you want them to
 – Were all the subjects classified into exposure groups using the same procedure

4. Was the outcome accurately measured to minimise bias? □ Yes □ Can’t tell □ No
 Look for measurement or classification bias:
 – Did they use subjective or objective measurements?
 – Do the measurements truly reflect what you want them to
 – Has a reliable system been established for detecting all the cases?
– Were the measurement methods similar in the different groups?
– Were the subjects and/or the outcome assessor blinded to exposure?

5. (a) Have the authors identified all important confounding factors?
☐ Yes ☐ Can’t tell ☐ No

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis?
☐ Yes ☐ Can’t tell ☐ No

List:

Consider:
– The restriction in design, and techniques e.g.
  modelling, stratified, regression, or sensitivity analysis
to correct, control or adjust for confounding factors.

6. (a) Was the follow up of the subjects complete enough?
☐ Yes ☐ Can’t tell ☐ No

(b) Was the follow up of the subjects long enough?
☐ Yes ☐ Can’t tell ☐ No

Consider:
– The good or bad effects should have had long enough
to reveal themselves
– The persons that are lost to follow-up may have different
  outcomes than those available for assessment
– In an open or dynamic cohort, was there anything special
  about the outcome of the people leaving, or the exposure
  of the people entering the cohort?
Appendix 1
CASP Tools

What are the results? (Section B)

7. What are the results of the study?

Consider:
– what are the ‘bottom line’ results?
– have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
– how strong is the association between the exposure and outcome (RR)?
– what is the absolute risk reduction (ARR)?

8. How precise are these results?

Consider:
– look at the confidence intervals, if given

9. Do you believe the results? □ Yes □ Can’t tell □ No

Consider:
– big effect is hard to ignore!
– can it be due to bias, chance or confounding?
– are the design and methods of this study sufficiently flawed to make results unreliable?

Will the results help locally? (Section C)

10. Can the results be applied to the local population? □ Yes □ Can’t tell □ No

Consider whether:
– a cohort study was the appropriate method to answer this question
– the subjects covered in this study could be different from your population in ways to cause concern
– your local setting differs much from that of the study
– you can quantify the local benefits and harms

11. Do the results of this study fit with other available evidence?
 □ Yes □ Can’t tell □ No

12. What are the implications of this study for practice?
   
   Consider:
   – one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
   – for certain questions observational studies provide the only evidence
   – recommendations from the observational studies are always stronger when supported by other evidence
Appendix 1

Critical Appraisal Skills Programme (CASP)

making sense of evidence

10 questions to help you make sense of case control study

How to use this appraisal tool

How to use this appraisal tool

Three broad issues need to be considered when appraising the report of a cohort study:

• Are the results of the trial valid? (Section A)
• What are the results? (Section B)
• Will the results help locally? (Section C)

The 11 questions on the following pages are designed to help you think about these issues systematically.

The first two questions are screening questions and can be answered quickly. If the answer to both is “yes”, it is worth proceeding with the remaining questions.

You are asked to record a “yes”, “no” or “can’t tell” to most of the questions. A number of italicised prompts are given after each question.

These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.
Are the results of the study valid? (Section A)

Screening Questions

1. Did the study address a clearly-focused issue? □ Yes □ Can’t tell □ No
   Consider if the question is ‘focused’ in terms of:
   – the population studied
   – the risk factors studied
   -is it clear whether the study tried to detect a beneficial or harmful effect?

2. Did the authors use an appropriate method to answer their question? □ Yes □ Can’t tell □ No
   – is a case control study an appropriate way of answering the question under the circumstances?
   – did it address the study question?

Is it worth continuing?

Detailed Questions

3. Were the cases recruited in an acceptable way? □ Yes □ Can’t tell □ No
   Look for selection bias which might compromise validity of the findings:
   – are the cases defined properly?
   – were the cases representative of a defined population?
   – was there an established reliable system for selecting all the cases?
   – are they incident or prevalent?
   – is there something special about the cases?
   – is the time frame of the study relevant to the disease/exposure?
   – was there a sufficient number of cases selected?
   – was there a power calculation?

4. Were the controls selected in an acceptable way? □ Yes □ Can’t tell □ No
   Look for selection bias which might compromise validity of the findings:
   – were the controls representative of a defined population?
   – was the non-response high? Could non-respondents be
Appendix 1

CASP Tools

different in any way?
– is there something special about the controls?
– are they matched/population based or randomly selected?
– was there a sufficient number of controls selected?

5. Was the exposure accurately measured to minimise bias? □ Yes □ Can’t tell □ No

Look for measurement or classification bias:
– was the exposure clearly defined and accurately measured?
– did they use subjective or objective measurements?
– do the measurements truly reflect what you want them to
– were the measurement methods similar in the cases and controls?
– did the study incorporate blinding where feasible?
– is the temporal relation correct?

6. (a) What confounding factors have the authors accounted for?

List:

List the ones you think might be important, that the author missed:
– genetic
– environmental
– socio-economical

(b) Have they taken account of the confounding factors in the design and/or analysis?
□ Yes □ Can’t tell □ No

Consider:
– the restriction in design, and techniques e.g.
modelling, stratified, regression, or sensitivity analysis
to correct, control or adjust for confounding factors.

7. What are the results of the study?

Consider:
– what are the ‘bottom line’ results?
– is the analysis appropriate to the design?
– how strong is the association between the exposure and outcome (odds ratio)?
– are the results adjusted for confounding, and
might confounding still explain the association?
– has adjustment made a big difference to the OR?

**What are the results? (Section B)**

8. How precise are these results?

   **How precise is the estimate of risk?**

   Consider:
   – look at the p-value
   – look at the confidence intervals, if given
   – have the authors considered all the important
     variables?
   – how was the effect of the subjects refusing to participate
     evaluated?

9. Do you believe the results?  □ Yes □ Can’t tell □ No

   Consider:
   – big effect is hard to ignore!
   – can it be due to bias, chance or confounding?
   – are the design and methods of this study sufficiently
     flawed to make results unreliable?

**Will the results help locally? (Section C)**

10. Can the results be applied to the local population? □ Yes □ Can’t tell □ No

   Consider whether:
   – the subjects covered in this study
   could be different from your population in ways
   to cause concern
– your local setting differs much from that of the study
– you can quantify the local benefits and harms

11. Do the results of this study fit with other available evidence?
□ Yes □ Can’t tell □ No

Remember:
– one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
– for certain questions observational studies provide the only evidence
– recommendations from the observational studies are always stronger when supported by other evidence