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Cancer Australia

Risk factors for endometrial cancer: A review of the evidence

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1 Introduction

1.1 Context

There are two major types of uterine cancer: endometrial cancer and uterine sarcoma. Endometrial cancers arise in the lining of the uterus whereas uterine sarcomas develop in the muscle of the uterus (myometrium) or the connective tissues that support the endometrium. Uterine sarcoma represents around 5% (3–7%) and endometrial cancer represents around 95%, of all uterine cancer.[1]

As the vast majority of uterine cancer cases are endometrial cancer, and as this is the cancer most frequently studied in terms of risk factors, endometrial cancer is the focus of this report. However the majority of health statistics in Australia are available only for uterine cancer overall, incorporating data from ICD–10 codes C54 (body of the uterus) and C55 (unspecified parts of the uterus).

It is estimated that uterine cancer will be the 5th most commonly diagnosed cancer among females in Australia in 2019, after breast, bowel, melanoma of the skin and lung cancer. In 2019, it is estimated that 3,115 new cases of uterine cancer will be diagnosed in Australia.[2]

Incidence of uterine cancer is increasing. The age–standardised incidence rate increased from 13.9 cases per 100,000 females in 1982 to 19.3 cases per 100,000 females in 2015. In 2019, it is estimated that there will be 562 deaths from uterine cancer in Australian women (AIHW, 2019). Uterine cancer incidence and outcomes vary by remoteness and socio–economic status and for Aboriginal and Torres Strait Islander peoples. In 2009–2013, Aboriginal and Torres Strait Islander women were 1.8 times more likely to be diagnosed with uterine cancer (30.0 per 100,000 females) compared to non–Indigenous Australian women (16.8 per 100,000 females).[3]

Uterine cancer survival in Australia has improved over time. Between 1986–1990 and 2011–2015, 5–year survival for women with uterine cancer increased from 77% to 83% compared to women in the general Australian population.[2]

There is a general lack of awareness among the Australian community of the modifiable risk factors for developing endometrial cancer, and there is a lack of current research to summarise the available evidence on risk factors for endometrial cancer in the Australian context.[4, 5] Recent evidence has demonstrated that even comparatively small modifications in potentially modifiable risk factors, such as overweight and obesity, can significantly reduce the risk of endometrial cancer.[6]

This report is intended primarily for health professionals and researchers seeking a more in–depth understanding of the nature and extent of the evidence base supporting various factors as being associated or not associated with the risk of endometrial cancer. This information aims to improve understanding of the current state of the evidence relating to risk and protective factors for endometrial cancer.

1.2 Endometrial cancer aetiology

1.2.1 Classification and histopathology

There are two types of endometrial cancer: type I (also known as endometrioid carcinoma) and type II (Table 1). Endometrioid carcinoma is the most common type of endometrial cancer and uterine malignancy overall. Endometrioid tumours are mostly adenocarcinomas that begin in the glandular cells of the endometrium. Endometrioid carcinomas are generally well– to moderately well–differentiated and are considered low–grade. This type of endometrial cancer has a favourable prognosis and typically presents at an early stage with abnormal uterine bleeding. Endometrioid carcinoma is associated with unopposed oestrogenic stimulation and may be preceded by an intraepithelial neoplasm (atypical and/or complex endometrial hyperplasia). This is thought to be due to the long–lasting unopposed oestrogen exposure leading to endometrial hyperplasia, which increases the chance of development of atypical hyperplasia and eventually Type I endometrial cancer.[7,8]

About 10% of endometrial cancers are type II lesions.[7] In contrast to type I tumours, type II tumours are not oestrogen driven and are mostly due to endometrial atrophy associated with factors such as increasing age. A precursor lesion is rarely identified. Type II endometrial cancers are either poorly differentiated endometrioid (grade 3) or non–endometrioid lesions such as serous carcinoma, clear cell carcinoma and mucinous carcinoma.[7] These tumours are often high–grade, have a poor prognosis, and a tendency to deeply invade the myometrium and metastasise.[9] Women with type II endometrial cancer are at high risk of relapse and metastatic disease.[7]

Table 1 Differences between type I and type II endometrial cancer. Adapted from Passarello et al. (2019)[10]

Characteristics	Type I	Type II
% of cases	80% to 90%	10% to 20%
Risk factors	Unopposed oestrogen	Age (postmenopausal women)
Precursor	Endometrial hyperplasia	Unknown, but often occurs in atrophic endometrium
Grade	Low	High
Histology	Endometrioid adenocarcinoma (grades 1 and 2)	Non–endometrioid (i.e. serous, clear cell) and poorly differentiated endometrioid (i.e. grade 3)
Molecular features	*PTEN* mutations; *KRAS* overexpression; microsatellite instability (MSI)	*KRAS* overexpression; *HER2* overexpression; *TP53* mutations
Metastasis	Uncommon, but often regional metastasis if this does occur	More common and can be regional and/or distant metastasis
Prognosis	Favourable	Not favourable

1.2.2 Pathogenesis and genetics

1.2.2.1 Hormonal mechanisms

The endometrium undergoes structural modification and changes in specialised cells in response to fluctuations of oestrogen and progesterone. Physiologically, oestrogen stimulates endometrial proliferation during the normal menstrual cycle. In contrast, progesterone offsets this effect by inhibiting endometrial proliferation and stimulating differentiation in preparation for implantation of an embryo.[11] Therefore the majority of endometrial cancers are caused by increased exposure to oestrogen, unopposed by progesterone. This causes continued proliferation of the endometrium, leading to endometrial hyperplasia and subsequent adenocarcinoma.[11] Increased endometrium exposure to oestrogen can be due to endogenous factors such as increased number of menstrual cycles and nulliparity, or by exogenous factors via hormone–related medications such as oestrogen–only menopausal hormone therapy and tamoxifen. Obesity and type 2 diabetes are associated with increased oestrogen levels due to aromatisation of androstenedione to oestrone in adipose tissue. In addition, insulin resistance associated with diabetes may play an independent role in the carcinogenesis of the endometrium.[12]

Type II endometrial cancers are not stimulated by oestrogen and usually do not express oestrogen or progesterone receptors.[13] Hence risk factors for type I and II cancers are not identical. For instance, women with type II tumours are more likely to be parous than nulliparous and risk of type II tumours due to obesity is less pronounced compared with type I.[14] Type II endometrial cancers typically arise in atrophic endometrium or an endometrial polyp in older adult women.

1.2.2.2 Genomic changes

The majority of endometrial carcinomas arise sporadically via acquired somatic alterations.[15]

Most sporadic endometrial cancers can be histologically classified as endometrioid, serous, or clear cell.[16] Each endometrial cancer histotype has a distinct natural history, clinical behaviour, and genetic aetiology. Endometrioid endometrial cancers are typified by frequent microsatellite instability (MSI), and somatic alterations within the PI3K pathway, the MAPK pathway, *CTNNB*(β–Catenin), and *ARID1A*(BAF250a). In sporadic endometrial tumours, MSI–positivity reflects an increased mutation rate resulting from somatic alterations in DNA mismatch repair (MMR) genes.[16] Type I cancers are also associated with overexpression of pro–tumourigenic *KRAS* oncogene and defects in DNA mismatch repair genes which result in microsatellite instability.[7]

Serous and clear cell endometrial cancers are typified by frequent genomic alterations affecting *TP53*, *PPP2R1A*, *HER–2/ERBB2*, *PIK3CA*, and *PTEN*; additionally, they display dysregulation of E–cadherin, p16, cyclin E, and BAF250a.[16] The genetic aetiology of clear cell endometrial cancers resembles that of serous endometrial cancers, but it remains relatively poorly defined.[16] Type II cancers are associated with mutations in the tumour suppressor *TP53* and overexpression of *HER2* oncogene which result in dysregulated proliferation and apoptosis.[7]

A small fraction of endometrial cancer cases are attributable to pathogenic changes in hereditary cancer predisposition syndrome genes, which confer a moderate to high lifetime

risk of endometrial and other syndromic cancers. These are predominantly high-risk pathogenic variants in the MMR genes causing Lynch syndrome, and very rarely, germline loss-of-function variants in the *PTEN* tumour suppressor gene causing Cowden syndrome.[15, 17] The hallmark of Lynch syndrome is MSI in tumour tissue which is caused by a failure of the DNA MMR.[18] MSI is reported in at least 75% of endometrial carcinomas associated with Lynch syndrome, while it occurs in 17% of sporadic endometrial carcinomas.

Non–Lynch syndrome or Cowden syndrome genes may also contribute to endometrial cancer risk, however currently only six genes included on clinical hereditary cancer panel tests have a proven association with endometrial cancer (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, and *PTEN*).[19, 20] In addition, multiple common genetic variants have already been identified to be associated with a very modest increase in endometrial cancer risk using genome-wide association studies (see references 14–17 in O'Mara et al.[21]), and the expectation is that such common variation will underlie a considerable proportion of the familial aggregation of the disease.[21]

1.3 Approach

This report provides an overview of current epidemiological knowledge about the evidence for the association of a broad range of exposures or factors and risk of endometrial cancer. It focuses on providing the best available, up-to-date evidence indicating whether factors of interest are or are not associated with risk of endometrial cancer.

Input and advice from a multidisciplinary Project Working Group and the Gynaecological Cancer Advisory Group, comprising epidemiological experts, health professionals, risk communication experts, and consumers, in consultation with Cancer Australia, has guided the choice of factors for inclusion and the underlying evidence review.

This review followed a systematic process to identify the evidence available for each factor. The evidence is classified (rated or graded) so that communication about the strength of the evidence for each factor can be consistent. A 'best estimate' of the magnitude of risk is reported for those factors for which there is sufficiently strong evidence—classified as either 'convincing' or 'probable'—that they are associated with an increased or decreased risk of endometrial cancer. For other factors, the evidence is classified as either 'suggestive', 'inconclusive' or 'evidence of no association'. Those that have been rated as 'suggestive' may be associated with risk of endometrial cancer, whereas factors for which the evidence base is 'inconclusive' have a limited basis from which to determine likelihood of an association. Where there is 'evidence of no association', such factors are unlikely to be associated with risk of endometrial cancer.

Readers should note that strength of evidence does not reflect the effect size of a factor or the direction of effect, and these elements should be considered as separate entities. For example, a factor can be of a convincing strength of evidence yet be associated with only a small increased risk of endometrial cancer.

While acknowledging the complexities and potential interrelations between risk factors, this report only considers risk factors individually. The risk estimates presented are for differences in single risk factors, with all other factors assumed to be equal.

2 Methods

2.1 Overview

This review aimed to determine whether there is sufficient evidence to support an association between various exposures, or factors of interest, and the risk of endometrial cancer; and to identify the magnitude of endometrial cancer risk—increased or decreased—for each factor where there is sufficiently strong evidence of an association.

Various international agencies including the World Cancer Research Fund /American Institute for Cancer Research (WCRF/AICR) and the International Agency for Research on Cancer (IARC), provide reports and monographs indicating the strength of the evidence for various factors of interest and risk of cancers (Appendix B). This review builds on the existing high level evidence reviews conducted by these authoritative bodies, where available.

Studies were selected according to the established hierarchy of evidence for aetiology studies, such that study type is an indicator of study quality. Further, other elements of the quality of the evidence, including study heterogeneity, publication bias and adjustment for confounders, were considered in determining the strength of the evidence.

An explicit process of classification of the evidence was undertaken to inform the reader about the likelihood of each factor of interest being either associated or not associated with risk of endometrial cancer.

2.2 Search strategy

Reviews of aetiology studies involve inclusion and exclusion criteria for 'population', 'exposure of interest' (independent variable), and 'outcome' (dependent variable).[22]

Population

- Healthy females of all ages independent of their exposure to any risk factors, for prospective cohort studies
- Women diagnosed with endometrial cancer of any age, and unaffected study participants, for retrospective cohort and case–control studies
- Women at risk of developing endometrial cancer, for randomised controlled trials
- Women generalisable to the Australian female population
- Other population sub–groups where relevant[i].

[i] e.g. Studies examining the effect of selective oestrogen receptor modulators (SERMs) on endometrial cancer risk may be limited to women with breast cancer or at high risk of breast cancer; or studies examining the effect of metformin on endometrial cancer risk may be only among women with diabetes.

Exposures

- A broad range of exposures—including exogenous and endogenous hormonal factors, lifestyle factors, family history & genetics, and medical factors—were considered for evidence review. The factors were identified and selected through an initial scoping of the literature and relevant, prominent national and international websites. A selection of factors known to be of particular interest to the community were included. The Project Working Group made the final selection of factors for inclusion, in consultation with Cancer Australia.

Outcome

- Endometrial cancer
- Uterine cancer
- Premenopausal endometrial cancer
- Postmenopausal endometrial cancer
- Endometrial cancer sub–types.

Search dates

If the WCRF/AICR had included the factor of interest in its most recently published systematic literature review[23] as part of the WCRF/AICR Continuous Update Project (CUP) then, for those factors, evidence was searched from the cut–off date (31 December 2012) of the CUP systematic literature review (CUP Endometrial SLR).[23] The International Agency for Research on Cancer (IARC) monographs were also searched for any evidence and considerations relating to the human epidemiological evidence in endometrial cancer. Where evidence was identified, relevant information was extracted and further evidence was only searched from IARC's most recent search date for that factor and risk of endometrial cancer.

For all other factors of interest, no limit to the earlier search date was used and

Early search dates were only used if there was a very limited amount of evidence (or no evidence) published more recently for a factor of interest. Occasionally, despite this review's emphasis on using the most current evidence, pre–2007 studies were included as background or to provide a fuller picture of the body of evidence.

For this review, the search for primary cohort studies focused only on the time since the last search date of the most recently published systematic review and meta–analysis or pooled analysis.

A top–up search was conducted in March 2019. A 'watching brief' for meta–analyses, pooled analyses and large cohort studies was maintained until July 2019.

Search terms

Bibliographic searches were performed on the Cochrane Library and Medline via OVID using MeSH terms and free text words:

Search date 8 January 2018
Ovid MEDLINE(R) Epub Ahead of Print, In–Process & Other Non–Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
(maligna$ or cancer$ or carcinoma or tumo?r).ti,ab.
(endomet$ or corpus uteri or uterine or uterus).ti,ab.
(risk or prognos$ or predict$ or inciden$ or associate$ or epidemiolo$ or dose–response or effect or adverse event or adverse effect).ti,ab.

and relevant exposure search terms. The PubMed database was initially searched to identify optimal search terms. Those used in the CUP Endometrial SLR[23] were used for the relevant factors.

The top up search was conducted in PubMed using a simple search string for each factor: '[factor]' AND ('endometrial cancer' OR 'uterine cancer' OR 'cancer of the uterus') AND ('risk OR incidence'). Citation tracking was also conducted in Google Scholar for the most recent pooled analysis, meta–analysis or large cohort study to identify any more recent studies.

2.3 Study selection

Inclusion criteria

Studies were included in this review if they:

- included published quantitative risk estimates and 95% confidence intervals (or some other measure of variability) of the association between each factor of interest and endometrial cancer. Odds ratios, hazard ratios, standardised incidence ratios, and risk ratios were all interpreted as relative risk given that all measures of relative risk are very similar when the risks are relatively small.
- included results from an epidemiologic study of one of the following types, in order of the generally accepted hierarchy of evidence for aetiologic studies:
  - meta–analysis, including pooled analysis
  - randomised controlled trial (RCT)
  - prospective cohort study
  - nested case–control study
  - retrospective cohort study
- human subjects
- articles published in English
- relevance to the Australian population.

In cases where this review retrieved many systematic reviews with meta–analyses addressing the same factor of interest, only the reviews that were most up–to–date, of the highest methodological quality, and included the largest number of primary studies (preferably RCTs or cohort studies) were selected. Pooled analyses of individual patient data (IPD) were prioritised as they are expected to be less at risk of residual confounding due to more uniform adjustment for important confounders across the study population compared to meta–analyses based on systematic review. In additon, meta–analyses/pooled analyses or primary

cohort studies which excluded women who had undergone hysterectomy were considered to be at lower risk of confounding.

Additional meta–analyses were included if they presented further information about a specific epidemiological element, such as different sub–exposures or a dose–response analysis, or analysis according to population subgroup such as menopausal status. If there was significant overlap in included studies and they did not provide additional evidence, then these additional meta–analyses were excluded. Overlap in studies contained within the various meta–analyses was not systematically explored for all factors.

Cohort studies published since the date of the most recent systematic review or pooled analysis were included.

Exclusion criteria

Studies were excluded from this review if they:

- were cross–sectional studies, individual case–control studies, narrative reviews, conference abstracts
- reported only on endometrial cancer mortality
- reported only on endometrial cancer clinical outcomes
- did not have full text available
- were not conducted in humans
- were not published in the English language
- did not provide quantitative risk estimates or only provided unadjusted risk estimates.

2.4 Data extraction and synthesis

After the search and study selection process, applicable full–text papers were retrieved for analysis.

Risk estimates were retrieved from the original article, along with 95% confidence levels. Odds ratio (OR) is a good approximation of the relative risk when the outcome occurs relatively infrequently (<10%). OR, rate ratios, standardised incidence ratios (SIR), hazard ratios (HR) and risk ratios were all interpreted as relative risk (RR) given that all measures of relative risk are very similar when the risks are relatively small. Where explicit adjustments were made, the type of statistic used and the variables of adjustment were noted.

Often, factors such as age, menopausal status, endometrial cancer subtype, and sometimes racial/ethnic identity, are reported as main factors of analysis, along with effects of particular exposures. This review reports significant main effects and interactions between exposures and these other variables are noted.

2.4.1 Assessment of evidence base

In this report, the methods used for assessing the strength of the body of evidence for each factor align with those used by the WCRF/AICR and follow the approach used previously in Cancer Australia's 2018 *Risk factors for breast cancer: A review of the evidence*. This system

was selected because it uses explicit criteria that are straightforward to apply and it enables integration of the judgements by the WCRF/AICR. The clearly defined classification criteria provide a systematic way to judge the strength of evidence relating to association with endometrial cancer risk.

The WCRF/AICR criteria require a range of factors to be considered, including quality of the studies, for example, whether the possibility of confounding, measurement errors and selection bias has been minimised (Appendix C, Table C.2). They also include the number of different study types and cohorts, whether there is any unexplained heterogeneity between results from different studies or populations, whether there is a dose–response relationship, and whether there is evidence of plausible biological mechanisms at typical levels of exposure. This review considered these elements of the nature of the evidence, i.e. the level, quality, consistency and quantity of evidence.

Table 2.2 shows the classification system used to classify the strength of the evidence for an association of a factor with an increase or decrease in the risk of endometrial cancer. The classifications are: 'convincing', 'probable', 'suggestive', 'inconclusive' or 'evidence of no association'.

Table 2.2 Criteria for classifying the strength of the evidence in terms of likelihood of association between an exposure (factor) and the risk of endometrial cancer

Classification	Generally required criteria
Convincing	*There is compelling and consistent evidence that the factor is associated with an increase or decreased risk of endometrial cancer. This classification includes factors that are causally associated with endometrial cancer as well as others that may be markers of underlying causes.* • Evidence from more than one study type and at least two independent cohort studies • No substantial unexplained heterogeneity within or between study types or in different populations regarding presence or absence of association, or direction of effect • Good quality studies to confidently exclude the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias • Presence of a plausible biological gradient ('dose–response') in the association. (Gradient need not be linear or in same direction across different levels of exposure, so long as this can be explained plausibly.) • Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes

Probable	*The factor is likely to be associated with risk[1] of endometrial cancer but the evidence is not as strong as for Convincing.* • Evidence from at least two independent cohort studies/at least five case–control studies • No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect • Good quality studies to confidently exclude the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias • Evidence for biological plausibility
Suggestive	*The evidence is suggestive of an association between the factor and risk[1] of endometrial cancer but there is not sufficiently strong evidence to be more certain.* • Evidence from at least two independent cohort studies/at least five case–control studies • Direction of effect is generally consistent, although some unexplained heterogeneity may be present • Evidence for biological plausibility
Inconclusive	*The evidence is too limited to determine the likelihood of an association with risk of endometrial cancer.* • This category represents an entry level, and is intended to allow any exposure for which there are sufficient concerns to warrant consideration, but where insufficient evidence exists to permit a grading. • The evidence might be limited in terms of the number of studies available, by inconsistency of direction of effect, by poor quality of studies (for example, lack of adjustment for known confounders), or by any combination of these factors.
Evidence of no association	*There is consistent evidence from good quality studies to show that the factor neither increases nor decreases the risk of endometrial cancer.* • Evidence from more than one study type • Evidence from at least two independent cohort studies • Summary estimate close to 1.0 for comparison of high versus low exposure categories • No substantial unexplained heterogeneity within or between study types or in different populations • Good quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding, and selection bias • Absence of a demonstrable biological gradient ('dose–response') • Absence of strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures lead to relevant cancer outcomes

2.4.2 Selection of best estimate of risk

A best estimate of risk was selected for all factors where the evidence for an association with endometrial cancer was classified as either 'convincing' or 'probable'. This estimate was selected as being representative of the data from the range of available studies, predominantly selected from a large pooled analysis or the most recent quality meta–analysis of a large number of (preferably) cohort studies. Consideration was given to the types of studies, the populations from which the estimates were derived, the precision of the estimates, and their relevance to exposure levels experienced among Australian women.

A comparative risk estimate, mostly relative risk, of appropriate exposures is provided in this report, together with the 95% confidence intervals. The source of the risk estimate is noted. The risk estimate may be presented for a continuous, binary or integer exposure, as relevant and as recorded in the published studies.

3 Endometrial cancer risk factors

3.1 General factors

3.1.1 Age

Evidence summary

Evidence classification: Convincing.

Age is a significant factor for developing uterine, and therefore endometrial (which comprises approximately 95% of uterine), cancer. The risk of uterine cancer increases with age, with the highest incidence rates in women aged 65–69 years in Australia. Uterine cancer primarily affects postmenopausal women with an average age at diagnosis of 60–65 years. However some women may develop uterine cancer under the age of 50, primarily due to risk factors such as hereditary genetic mutations and obesity.

Using 2015 incidence rates in Australia, women aged 60–64 years are at approximately 8 times increased risk of uterine cancer compared with women aged 40–44 years. Women aged 65–69 years are at approximately 5 times increased risk of uterine cancer compared with those aged 45–49 years.[2]

Incidence

Over 65% of all uterine cancers, of which the vast majority (approximately 95%) are endometrial cancers, in Australia are diagnosed in women when they are aged 60 years or over. The average age at first diagnosis of uterine cancer in women is 64.8 years, based on 2015 data.

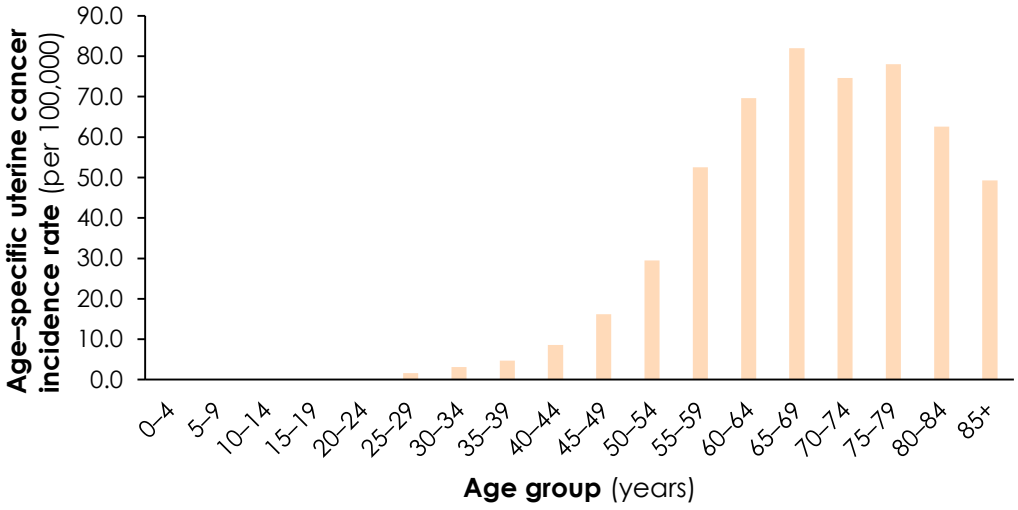

Figure 1 Age–specific incidence of uterine cancer in Australia, by age group, 2015

Source: Australian Institute of Health and Welfare. Australian Cancer Incidence and Mortality (ACIM) books 2019 [Available from: https://www.aihw.gov.au/reports/cancer/acim–books/contents/acim–books.] Last updated 26 July 2019

In Australia, the uterine cancer age–specific incidence rate increases steeply from age 40–44 years (8.6 per 100,000 in 2015) to a peak at age 65–69 years (82.0 per 100,000 in 2015) before gradually decreasing (78.0 per 100,000 for 75–79 years and 49.3 per 100,000 for 85+ years in 2015) (Figure 1; data taken from AIHW).[2] This equates to a risk of diagnosis before age 75 as 1 in 59, and before age 85 as 1 in 42. These results represent an increased incidence of uterine cancer in Australia since 1984: from 1 in 79 before age 75 and 1 in 60 before age 85. This increased incidence is partly due to the ageing population.

The incidence of uterine cancer has increased over the past 20 years among all age groups (Figure 2). The incidence rates in women aged 40–44 years increased from 5.7 per 100,000 women in 1995 to 8.6 per 100,000 women in 2015. The respective incidence rates in women aged 50–54 years and 60–64 years increased from 25.9 to 29.5 per 100,000 women and from 52.1 to 69.6 per 100,000 women.

The upward trend in incidence of uterine cancer has paralleled an increase in obesity[3] in Australian women, as measured by body mass index[24] and waist circumference[25], as well as an increased incidence of diabetes[26]. Changes in prevalence of reproductive and other factors associated with an increased risk of uterine cancer, such as lower parity and insufficient physical activity, are also likely associated with the trends over time.

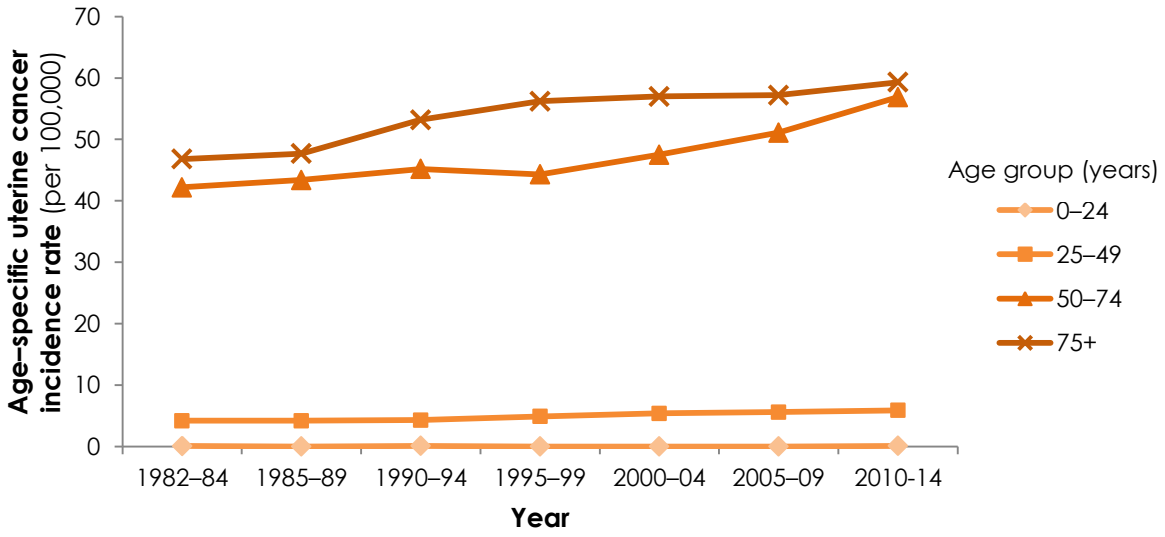

Figure 2 Age–specific incidence of uterine cancer in Australia over time, 1982–2014, and different age groups

Source: Australian Institute of Health and Welfare. Australian Cancer Incidence and Mortality (ACIM) books 2019 [Available from: https://www.aihw.gov.au/reports/cancer/acim–books/contents/acim–books.] Last updated 26 July 2019

3.2 Family history & genetics

3.2.1 Family history of endometrial cancer or colorectal cancer

Evidence summary

Evidence classification—Convincing: Family history of endometrial cancer.

Evidence classification—Convincing: Family history of colorectal cancer (in the context of Lynch syndrome).

There is convincing evidence that a family history of endometrial cancer or a family history of colorectal cancer in the context of Lynch syndrome, is associated with an increased risk of endometrial cancer.

A meta–analysis of 16 studies reported an increased risk of endometrial cancer in women with a first–degree relative (FDR) with a history of endometrial cancer compared to women with no FDR with a history of endometrial cancer (RR 1.82, 95%CI 1.65–1.98).[27] An increased risk is observed within and outside of families with Lynch syndrome. The cumulative risk of endometrial cancer to age 70 years in women with a FDR with a history of endometrial cancer is estimated to be 3.1%, compared to 1.8% in the general population.[27] The population–attributable risk for a first–degree family history of endometrial cancer was estimated to be 3.5% (95%CI 2.8–4.2).[27]

The meta–analysis by Win et al. (2015) indicated that women with a FDR with a history of colorectal cancer had an increased risk of endometrial cancer compared with those without a family history (RR 1.17, 95%CI 1.03–1.31).[27] However, the association is likely only observed among Lynch syndrome families.

Background

Factors suggestive of a genetic hereditary contribution to cancer include an increased incidence of the cancer among individuals with a family history of these cancers, multiple family members affected with these and other cancers, and a pattern of cancers compatible with autosomal dominant inheritance.

While most women who develop endometrial cancer do not have a family history of the disease, it has been shown that family history, either on the maternal or paternal side and in first– or second–degree relatives, can influence endometrial cancer risk. First–degree relatives are an individual's mother, sisters and daughters. Second–degree relatives are an individual's aunts, grandmothers, grandchildren, nieces and half siblings.

Inherited genetic factors contribute to the mechanism for the association between increased endometrial cancer risk and family history of endometrial cancer.[20] These genetic factors may include common genetic variants identified by genome-wide association studies to be associated with modest levels of risk[21], and rarer genetic variants conferring high or moderate increased risk of cancer (discussed in sections 3.2.2 and 3.2.3). Shared environmental factors, such as obesity resulting from common lifestyle and dietary factors, may also contribute to the association between family history and endometrial cancer risk.[20]

Recent evidence

Family history of endometrial cancer

Of the fourteen studies (4 cohort and 10 case–control) assessing the association between a family history of endometrial cancer and risk of endometrial cancer in the meta–analysis by Win et al. (2015)[27], nine reported clear evidence of an increased risk of endometrial cancer for women with at least one FDR with endometrial cancer compared with those without a family history. In all studies combined, the RR for endometrial cancer in women with one affected FDR compared with women with no affected relatives was 1.82 (95%CI 1.65–1.98). The cumulative risk of endometrial cancer to age 70 years was 3.1% (95%CI 2.8–3.4) for women with a first–degree family history of endometrial cancer compared with 1.8% (CI not reported) for women in the general population (in the US) and 1.7% for women without a first–degree family history of endometrial cancer. However there was considerable imprecision in the study–specific estimates that contributed data to this meta–analysis, with point estimates ranging from1.2 to 5.0 for either case–control or cohort studies. The population–attributable risk for a first–degree family history of endometrial cancer was estimated to be 3.5% (95%CI 2.8–4.2).

Three studies (Cook et al. 2013, Bermejo et al. 2004, Bharati et al. 2014)[28-30] included in the meta–analysis by Win et al. (2015)[27] assessed the risk of endometrial cancer associated with a first–degree relative (FDR) after excluding Lynch syndrome families and all reported significant associations with a family history of endometrial cancer. Win et al. (2015)[27] concluded that these studies suggest the existence of inherited genetic defects other than MMR gene mutations that may predispose women to endometrial cancer.

The age at diagnosis of endometrial cancer in a FDR was assessed in two of the included studies with a large cohort study reporting a higher risk of endometrial cancer for women with a FDR with younger age at diagnosis of endometrial cancer. Only one study assessed the risk of endometrial cancer by the number of affected FDRs and this study reported a higher risk of endometrial cancer for women with a higher number of affected FDRs. A meta–analysis to generate pooled estimates of the association by the number of affected relatives, degree and type of relatedness, and age at diagnosis in the relatives, was not possible.

Johnatty et al. (2017)[17] examined the risk of endometrial cancer associated with a family history of endometrial cancer and other cancers, using data from the population–based Australian National Endometrial Cancer Study (ANECS). Self–reported family cancer history was available for 1,353 endometrial cancer patients and 628 controls. Risk of endometrial cancer in women with endometrial cancer in at least one FDR or one second degree relative (SDR) was OR 3.39 (95%CI 2.08–5.53).[17] Consideration of colorectal, breast and other syndrome cancers reported in relatives did not improve the risk prediction associated with report of endometrial cancer in a relative, suggesting that the risk estimates and trends for combinations of cancers are mostly driven by report of endometrial cancer in a relative. Report of endometrial cancer in ≥1 FDR or SDR was associated with increased risk of endometrial cancer ($P=3.8\times10^{-7}$), independent of lifestyle risk factors. There was a trend in increasing endometrial cancer risk with closer relatedness and younger age at endometrial cancer diagnosis in relatives ($P_{Trend}=4.43\times10^{-6}$), and with increasing numbers of Lynch syndrome–associated cancers in relatives ($P_{Trend}\leq0.0001$). Reported endometrial cancer in FDRs or SDRs remained associated with endometrial cancer risk after conservative correction for potential misreported family history (OR 2.0, 95%CI 1.24–3.37). The strongest predictor of

endometrial cancer risk was closer relatedness and younger endometrial cancer diagnosis age in ≥1 relative. Associations remained significant irrespective of proband MMR status, and after excluding MMR pathogenic variant carriers, indicating that Lynch syndrome genes do not fully explain familial endometrial cancer risk.

Family history of colorectal cancer

Of the nine studies (3 cohort and 6 case–control) assessing the association between a family history of colorectal cancer and risk of endometrial cancer included in the meta–analysis by Win et al. (2015)[27], only one case–control study reported a statistically significant increase in risk of endometrial cancer for women with a family history of colorectal cancer. Two other case–control studies reported a borderline association. Overall, women with a FDR with colorectal cancer had a slightly increased risk of endometrial cancer compared with those without a family history (RR 1.17, 95%CI 1.03–1.31).

Three studies (Cook et al. 2013, Bermejo et al. 2004, Bharati et al. 2014)[28-30] estimated risk of endometrial cancer associated with a family history of colorectal cancer after excluding Lynch syndrome families, and all reported no evidence of association with a first–degree family history of colorectal cancer overall. However, the study by Bharati et al. (2014)[30] reported an increased risk of endometrial cancer for women with a FDR with early–onset colorectal cancer, diagnosed before age 50 years without a *MMR* gene mutation, of RR 1.48 (95%CI 1.15–1.91).

Yu et al. (2019)[31] conducted a study assessing the associations of familial colon and rectal cancers with other cancers. The study was based on the Swedish Family–Cancer Database which includes around15.7 million Swedish individuals born in 1932 or later with 1.8 million people diagnosed with cancer. The incidence rate ratio (IRR) of endometrial cancer increased when FDRs had colon cancer (at approximately 1% level) (RR 1.27, 95%CI 1.14–1.41) but not rectal cancer (RR 1.00, 95%CI 0.89–1.13).[31] After removing Lynch syndrome cancer families, the relative risk of endometrial cancer was no longer significant.

3.2.2 Mismatch repair gene mutations

Evidence summary

Evidence classification: Convincing.

There is convincing evidence that having a mutation in a mismatch repair (MMR) gene *MLH1, MSH2, MSH6* or *PMS2* (Lynch syndrome), is associated with an increased risk of endometrial cancer. The cumulative lifetime risk of endometrial cancer to age 70 years associated with carrying a MMR mutation has been estimated as 33% (95%CI 16%–57%).[32] The risk of endometrial cancer varies from 15–71% depending on the specific MMR gene mutation and genotype. Compared with other MMR genes, mutations in the *PMS2* gene is associated with the lowest risk of endometrial cancer.

Women with Lynch syndrome are more likely to develop endometrial cancer at a younger age (mean age 46–54 years) than women without Lynch syndrome (61 years).[33]

Background

Lynch syndrome, previously known as hereditary non–polyposis colorectal cancer, is an autosomal dominant disorder that is caused by a mutation in one of several DNA mismatch repair genes including *MLH1*, *MSH2, MSH6*, and *PMS2*. Deficiency in the DNA mismatch repair (MMR) due to gene mutations results in replication errors and loss of regulated cellular proliferation which drives tumourigenesis.[34] This highly conserved system is responsible for correcting insertion and deletion errors that occur during genomic replication. Loss of MMR functioning, termed MMR deficiency (MMRd), leads to microsatellite instability (MSI), a hypermutated phenotype, and increased cancer susceptibility.[35]

Mutations in *MSH2* or *MLH1* are thought to account for approximately 90 percent of the heterozygous germline mutations that have been identified in patients with Lynch syndrome, *MSH6* mutations are thought to account for most of the remainder, and *PMS2* mutations have been described in relatively few Lynch families.

Germline deletions of the last few exons of the *EPCAM* (epithelial cell adhesion molecule) gene are also involved in the aetiology of Lynch syndrome.[36] In a subset of Lynch syndrome patients *MSH2* has been found to be specifically inactivated in cell lineages exhibiting *EPCAM* expression.[37] Deletions of the last few exons of *EPCAM* (3'end deletions) constitute a distinct class of mutations associated with Lynch syndrome. The risk of endometrial cancer in the entire group of *EPCAM* deletion carriers is significantly lower than that in *MSH2* mutation carriers. Only those deletions extending close to the *MSH2* promoter have an increased risk of endometrial cancer.[38]

Loss of MMR can also occur in sporadic cancers.[39] Somatic epigenetic changes such as promoter hypermethylation can silence gene expression and result in microsatellite instability (MSI). Approximately 20 percent of endometrial cancers are MSI–positive; less than 5 percent are thought attributable to Lynch syndrome.[40]

Lynch syndrome occurs in the population with a prevalence of 1 in 300 to 1 in 1,000 individuals. Defective MMR genes (MLH1 and MSH2) are thought to be present in between 1 out of 370 to 3100 people between the ages of 15 to 74.[40]

Recent evidence

Johnatty et al. (2017)[17] showed that carriage of a pathogenic variant in an MMR gene only partly accounts for risk of endometrial cancer associated with reported family history indicating that additional genetic risk factors remain to be identified.

Germline defects in MMR genes underlie the aetiology of less than 5% of endometrial cancer at the population level (summarised in Buchanan et al. 2014).[41] Spurdle et al. (2017)[20] also indicated that, taken together, loci identified to date are expected to account for ~5% of the familial RR of endometrial cancer. An earlier systematic review and meta–analysis by Win et al. (2015)[27] indicated that Lynch syndrome accounts for between 2% and 6% of all endometrial cancers. In an unselected population of endometrial cancer patients, Ring et al. (2016)[19] indicated that the prevalence of MMR genes mutations associated with Lynch syndrome was 5.8%; whereas the prevalence of other pathogenic genetic mutations was 3.4%. A systematic review and meta–analysis by Ryan et al. (2019)[35] included data from 53 published articles involving 12,633 patients with endometrial cancer and showed that

approximately 3% of endometrial cancer cases can be attributed to Lynch Syndrome. However, there was notably high heterogeneity across the studies reflecting varying quality and rigour of the included studies, some of which had small numbers of participants and were subject to bias, and overall limiting the strength of the study conclusions.

Long et al. (2019)[42] found that among 1170 unselected patients with endometrial cancer, Lynch syndrome mutations (*MSH2, MSH6, PMS2, MLH1*) were identified in 1.4% of type I and 1.6% of type II cases, including 1.5% of uterine sarcomas. Non–Lynch syndrome cancer predisposition gene mutations occurred in 2.8% (24/849) patients with type I endometrial cancer compared to 3.7% (12/321) patients with type II endometrial cancer, including 5.2% (7/135) patients with uterine serous cancers.[42]

The risks associated with carrying an MMR gene mutation have been most often expressed as cumulative incidences or risks, generally to age 70 years. For example, a large study by Bonadona et al. (2011)[32] examining 537 families with MMR mutations (*MLH1, MSH2, MSH6, PMS2*) across 40 French cancer genetics clinics, reported that the cumulative risk of Lynch syndrome–associated endometrial cancer by age 70 years was 33% (95%CI 16%–57%). It was indicated that ascertainment bias was accounted for in the analyses.

The four MMR gene mutations have different penetrance and expressivity and the cumulative incidences/risks for endometrial cancer to age 70 for the different mutations have been estimated across a number of studies:

- *MLH1*:
    - 34% (24–44%) Møller et al. (2017)[43]
    - 30% (18–45%)Dowty et al. (2013)[44]
    - 27% (14–38%) Hendriks et al. (2004)[18]
- *MSH2*:
    - 51% (33–69%) Møller et al. (2017)[43]
    - 18% (9–34%) Dowty et al. (2013)[44]
    - 40% (21–54%) Hendriks et al. (2004)[18]
- *MSH6*:
    - 49% (25–74%) Møller et al. (2017)[43]
    - 26% (18–36%) Baglietto et al.(2010)[45]
    - 71% (50–83%) Hendriks et al. (2004)[18]
- *PMS2*:
    - 24% (0–53%) Møller et al. (2017)[43]
    - 15% (6–35%) Senter et al. (2008)[46]
    - 13% (7–24%) Ten Broeke et al. (2018)[47]

Dunlop et al. (1997)[48] provided a cumulative lifetime risk of uterine cancer to age 70 years of 42% among 35 female MMR gene mutation carriers (*MLH1* and *MSH2*) identified through a population–based strategy, and it was noted that this exceeded that for colorectal cancer in females. Other estimates for *MLH1* and *MSH2* mutation carriers include 54% (Hampel et al. 2005)[49] and 54.1% (Aarnio et al. 1999)[50], as cited by Meyer et al. (2009)[51].

In the study by Møller et al. (2017)[43], endometrial cancers were detected from 25 years onwards in *MLH1* and *MSH2* mutation carriers, and from about 40 years in *MSH6* and *PMS2* carriers. Bonadona et al. (2011)[32] indicated that the estimated cumulative risk did not exceed 2%, irrespective of gene mutation, before age 40 years.

Few studies have reported relative risks. Senter et al. (2008)[46] indicated that, based on incidence rates in the North American population, the Hazard Ratio of endometrial cancer (to age 70 years) associated with carrying an MMR gene mutation was 7.5 (95%CI 2.9–20.0).

The mean age at diagnosis of endometrial cancer in women with Lynch syndrome is 46–54 years compared with a mean age of 61 years in other women.[52]

3.2.3 *PTEN* gene mutation

Evidence summary

Evidence classification: Convincing.

There is convincing evidence that having a *PTEN* gene mutation within the context of a personal/family history of Cowden syndrome is associated with an increased risk of endometrial cancer. The cumulative lifetime risk of endometrial cancer to age 70 years has been variously estimated as 19% (95%CI 10–32%)[53] and 28.2% (95%CI 17.1–39.3%)[54]. The risk of endometrial cancer among *PTEN* mutation carriers is highest among younger age groups and the risk compared to women without a *PTEN* mutation has been estimated as 2.9 among women aged ≥50 years.[54] Because of the low prevalence of *PTEN* pathogenic variants in the population, the proportion of endometrial cancer attributable to Cowden syndrome is small.[55]

Background

The *PTEN* gene codes for a protein involved in regulating a cell survival signaling pathway–phosphatase and tensin homolog. *PTEN* acts as a tumour suppressor gene, which helps regulate cell division by keeping cells from growing and dividing too rapidly or in an uncontrolled way. The PTEN protein is a phosphatase that removes phosphate groups from other proteins. It is involved in several functions that may be involved in development of cancer, including DNA repair, cellular senescence, cell migration and maintaining the stability of the cell's genetic information.[56, 57]

Inherited, or germline, mutations in the *PTEN* gene are associated with the PTEN hamartoma tumour syndrome (PHTS) that encompasses several heritable disorders including Cowden syndrome. Cowden syndrome is an autosomal dominant inherited disorder characterised by multiple benign hamartomas—typically on the skin, mucous membranes, and the intestine—and a susceptibility to several other cancers.[20] Endometrioid histology is reported to be the most prevalent histologic type in individuals who carry a *PTEN* pathogenic variant.

Somatic mutations of *PTEN* are common in sporadic endometrial cancers.[20, 39] Pathogenic mutations in *PTEN* are estimated to occur in approximately 1 in 200,000 individuals.[58]

Recent Evidence

Spurdle et al. (2017)[20] note that germline *PTEN* mutations do not account for a significant proportion of genetic attributable risk for endometrial cancer. For example, in the retrospective cohort study by Black et al. (2005)[39] among 240 women with endometrial cancer, no pathogenic *PTEN* variant was identified. Spurdle et al. (2017)[20] also cite three

other studies reporting results of multigene cancer panel testing of unselected or familial endometrial cancer patients and note that only a single *PTEN* pathogenic variant was identified, and that this patient reported a clinical history consistent with Cowden syndrome.

Riegert–Johnson et al. (2010)[53] reported that, in a meta–analysis of 210 patients with Cowden syndrome, the cumulative lifetime risk of endometrial cancer (to age 70 years) associated with carrying a *PTEN* mutation was 19% (10–32%). The authors noted that ascertainment biases and publication biases may have artificially elevated the risks.

Tan et al. (2012)[54] in a study of 368 participants who were asymptomatic family members of people with Cowden syndrome with pathogenic *PTEN* mutations identified through screening, estimated the cumulative lifetime risk to age 70 years to be 28.2% (95%CI 17.1–39.3%) and the SIR to be 42.9 (95%CI 28.1–62.8). PTEN–related endometrial cancer risk began, in this study, at age 25. Relative risk of endometrial cancer among *PTEN* mutation carriers compared to the general population was substantially higher among younger age groups and decreased to RR 2.9 among women aged ≥50 years.[54]

In a study among 154 individuals with Cowden syndrome and a pathogenic *PTEN* mutation, Bubien et al. (2013)[59] indicated that three cases of endometrial cancer were reported compared to an expected 0.06 cases in the general population, and the estimated SIR was 48.7 (95%CI 9.8–142.3).

Pilarski et al. (2013)[60] indicated that these three studies were subject to both underestimation and overestimation, the former due to inclusion of women with a previous hysterectomy and the latter due to ascertainment biases.

Spurdle et al. (2017)[20] cite three reports of adolescent onset endometrial cancer in the context of a personal and/or family history of Cowden syndrome which have been attributed to pathogenic germline variants in *PTEN*.

3.3 Endogenous hormones

3.3.1 Age at menarche

Evidence summary

Evidence classification: Convincing

There is convincing evidence that younger age compared to older age at menarche is associated with an increased risk of endometrial cancer[ii]. The increased risk for every 2 years younger at menarche is estimated to be 1.04 (95%CI 1.02–1.06).[61]

Background

The association between age at menarche and risk of endometrial cancer is likely attributable to the 'unopposed oestrogen' hypothesis whereby exposure to oestrogen, in the absence of sufficient progestin, leads to increased mitotic activity, DNA replication, and somatic mutations of endometrial cells that may result in malignant transformations. Conversely, older age at menarche might decrease the risk of endometrial cancer by reducing a woman's lifetime number of ovulations and thus exposure to endogenous oestrogen and progesterone.[61]

Recent evidence

Three studies were identified for inclusion, two pooled analyses[14, 62] and one meta–analysis[61]. The two pooled analyses included studies participating in the Epidemiology of Endometrial Cancer Consortium (E2C2)[iii].

The meta–analysis by Gong et al. (2015)[61] included eight prospective cohort studies and showed that the oldest categories of age at menarche (oldest age category ranged from ≥15 to 17 years) compared with the youngest categories of age at menarche (youngest age category ranged from <11 to 13 years) was associated with a decreased risk of endometrial cancer (RR 0.68; 95%CI 0.58–0.81; with moderate heterogeneity). Similar results were reported for various subgroup analyses (based on duration of follow–up, number of cases, exposure assessment and study population), and inclusion of studies adjusting for different confounders (BMI, parity, oral contraceptive use, exogenous hormone use, menopausal status and smoking status). A dose–response analysis indicated a 4% decreased risk per 2–year older age at menarche (RR 0.96, 95%CI 0.94–0.98; 6 studies). This is equivalent to an increased risk of 1.04 (95%CI 1.02–1.06) for every 2 years younger at menarche.

[ii] The pooled analyses and meta–analyses have generally reported on the converse, i.e. that an older age at menarche is associated with a decreased risk of endometrial cancer.

[iii] E2C2 is an international consortium formed in 2006 to provide a collaborative environment to address questions around endometrial cancer by pooling data from existing studies that would be underpowered in individual studies. To date, the Consortium includes data from more than 40 studies from the United States, Canada, Europe, Asia and Australia.

The pooled analysis by Setiawan et al. (2013)[14] excluded women without an intact uterus from the control group and provided sensitivity analysis based on study type and source of histological classification. Twenty–four studies (10 cohort and 14 case–control studies) were included and in the main analysis, older age at menarche (11–12 years, 13–14 years and ≥15 years) compared to younger age at menarche (<11 years) was associated with a decreased risk of Type 1 endometrial cancer (OR 0.89, 95%CI 0.80–0.99; OR 0.85, 95%CI 0.77–0.94 and OR 0.71, 95%CI 0.63–0.80; respectively; p trend<0.0001). Corresponding risk estimates for type II endometrial cancer were slightly lower. An analysis restricted to postmenopausal women who had never used menopausal hormone therapy yielded similar results. Similar risk estimates were reported for other subgroup analyses including tumour grade, study type (cohort or case–control) and histology source (pathology review or registry); although in many cases the findings were no longer statistically significant.

Cote et al. (2015)[62] examined differences in risk of endometrial cancer associated with age at menarche for white versus black American women across seven cohort studies and four case–control studies. Four of the seven cohort studies and all four case–control studies were also included in the analyses by Setiawan et al. (2013)[14]. A significantly decreased risk of endometrial cancer was reported for white women who were ≥16 years old at menarche compared to those who were 12–13 years old at menarche (OR 0.89, 95%CI 0.82–0.97), however the association for black women was not significant (OR 0.94, 95%CI 0.73–1.22).

3.3.2 Age at menopause

Evidence summary

Evidence classification: Convincing.

There is convincing evidence that older age compared to younger age at menopause is associated with an increased risk of endometrial cancer. One pooled analysis and two large prospective cohort studies have provided similar estimates of risk and evidence of a dose–response relationship. The increased risk has been estimated as 1.06 (95%CI 1.04–1.09) for every year older that menopause occurs.[63]

Background

Menopause is signalled by 12 months since last menstruation. The median age of menopause in Australian women is 51 years.[64] During natural menopause, the body's production of oestrogen and progesterone decreases.

The association between age at menopause and risk of endometrial cancer can be explained by plausible biological mechanisms. Late menopause can potentially result in an increase in the number of ovulatory cycles a woman experiences in her lifetime. This in turn may increase the lifetime exposure of the endometrium to circulating endogenous oestrogen which plays a role in the development of endometrial cancer. Moreover, progesterone deficiency associated with anovulatory cycles that are more common during late reproductive life may also contribute to endometrial cancer risk.[65]

Recent evidence

One pooled analysis[66] and two prospective cohort studies were identified.[63, 65]

Laaksonen et al.(2019)[66] analysed pooled data from six prospective Australian cohort studies including 160,555 women followed for a median of 4.9 years (510 cases). After adjustment for age, study, body fatness, oral contraceptive use, height and nulliparity, older age at menopause was associated with an increased risk of endometrial cancer (HR 1.07, 95%CI 1.04–1.10 per year older at menopause). The risk of endometrial cancer in women aged ≥55 years at menopause was 1.81 (95%CI 1.27–2.59) compared with women who reached menopause at <55 years.

Dossus et al. (2010)[63] analysed data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Among 302,618 women followed for a mean period of 8.7 years, 1,017 cases of endometrial cancer were identified. In an analysis stratified by age and centre and adjusted for BMI, physical activity, baseline alcohol consumption, diabetes, smoking status, and level of education, compared with age at menopause of ≤50 years, older ages at menopause were associated with increased risks of endometrial cancer (HR 1.32, 95%CI 1.04–1.68; HR 1.49, 95%CI 1.18–1.89; HR 2.20, 95%CI 1.61–3.01; for ages at menopause of 51–52 years, 53–55 years, >55 years, respectively). A dose–response analysis showed that for every year older that menopause occurs, the risk of endometrial cancer was increased by 6% (HR 1.06, 95%CI 1.04–1.09)[iv].

Similar findings were reported by Karageorgi et al. (2010)[65] in an analysis of data from the Nurses' Health Study. Among a cohort of 121,700 female nurses, 778 (658 postmenopausal) cases of Type 1 endometrial cancer were identified over a follow–up period of 28 years. Compared with women who reached menopause between the ages of 45–49 years, the increased risk for women who reached menopause at age 50–54 years was 1.49 (95%CI 1.22–1.82) and for women aged ≥55 years at menopause the increased risk was 1.53 (95%CI 1.13–2.06). No association with risk of endometrial cancer was observed in women who reached menopause at age <45 years compared to those who reached menopause between the ages of 45–49 years (RR 1.22, 95%CI 0.85–1.75).

3.3.3 Breastfeeding

Evidence summary

Evidence classification: Probable.

Breastfeeding is probably associated with a decreased risk of endometrial cancer. A pooled analysis of a large number of studies has reported a modest decreased risk of endometrial cancer associated with ever versus never breastfeeding, although this finding is not observed across meta–analyses. There is consistent evidence of a dose–response relationship, with longer versus shorter durations of breastfeeding associated with decreased risk, although this

[iv] Converted from per year younger age at menopause: HR 0.94 (95%CI 0.92–0.96) reported by Dossus et al. 2010.

relationship may not be linear. The decreased risk of endometrial cancer has been estimated as 0.97 (95%CI 0.96–0.98) per 3 months of total breastfeeding.[67]

The proportion of endometrial cancers (population attributable fraction) that could be prevented by breastfeeding for greater than or equal to 6 months per child is estimated to be 11% among parous women and approximately 9% for all women.[67]

Background

Breastfeeding can suppress gonadotrophin–releasing hormone thereby inhibiting ovarian follicular growth and reducing oestradiol levels to within the postmenopausal range. At such low oestrogen levels, endometrial cell proliferation virtually ceases.[67] Also, lactational amenorrhoea results in a lower oestrogen exposure, which has been related to decreased proliferative and carcinogenic effects.[68]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR 2018)[69] did not include 'breastfeeding' in the most recent update. The WCRF/AICR systematic literature review (SLR) of evidence to December 2012 (CUP Endometrial SLR)[23] did not identify any new studies on breastfeeding since the 2005 SLR, when only one study by Kvale et al. (1988)[70] had been identified.

Recent evidence

Four studies were identified for inclusion, one was a pooled analysis[67] and three were meta–analyses[68, 71, 72]. These all included summary estimates that had been adjusted for potential confounding.

The pooled analysis by Jordan et al. (2017)[67] included 17 studies (3 cohort and 14 case–control studies; 17421 controls, 8981 cases) participating in the Epidemiology of Endometrial Cancer Consortium (E2C2[v]). In the main analysis, ever versus never breastfeeding was associated with a decreased risk of endometrial cancer (OR 0.89, 95%CI 0.81–0.98; with evidence of moderate heterogeneity). Increasing duration of breastfeeding beyond three months was associated with a decreased risk of endometrial cancer (OR per 3 months total breastfeeding 0.97, 95%CI 0.96–0.98), although the association was not clearly linear and the decline in risk was smaller beyond 6–9 months of breastfeeding duration. The association of ever breastfeeding and decreased risk of endometrial cancer did not vary significantly by parity, menopausal status, body mass index or endometrial cancer subtype; or by study type.

The three meta–analyses (Ma et al. 2018 (searched to Feb 2015), Wang et al. 2015, Zhan et al. 2015)[68, 71, 72] included nearly all of the same studies (3 cohort studies and 12 case–control studies were included across the three meta–analyses) resulting in similar, non–statistically significant, risk estimates for a comparison of ever versus never breastfeeding and decreased

[v] E2C2 is an international consortium formed in 2006 to provide a collaborative environment to address questions around endometrial cancer by pooling data from existing studies that would be underpowered in individual studies. To date, it includes data from more than 40 studies from the United States, Canada, Europe, Asia and Australia.

risk of endometrial cancer (0.91 95%CI 0.75–1.09, with evidence of significant heterogeneity; 0.85, 95%CI 0.61–1.20; and 0.88, 95%CI 0.72–1.06; respectively).

Ma et al. (2018)[68] reported that the longest duration compared with the shortest duration of breastfeeding was associated with a decreased risk of endometrial cancer of 0.61 (95%CI: 0.44–0.85; with evidence of moderate heterogeneity). Wang et al. (2015)[71] also reported a decreased risk of endometrial cancer when the longest duration of breastfeeding was compared with the shortest duration of breastfeeding (RR 0.71, 95%CI 0.53–0.95).

A dose–response analysis by Ma et al. (2018)[68] based on 2 cohort and 5 case–control studies indicated a 7% decrease in endometrial cancer risk for every 6–month increase in total breastfeeding duration (RR 0.93, 95%CI 0.88–0.97; evidence of moderate heterogeneity). When studies were stratified by adjustment for specific confounders, significant inverse associations were still observed in all subgroups, except for the subgroup adjusted for use of oral contraceptives (RR 0.52, 95%CI 0.23–1.16; moderate heterogeneity possibly due to small number of studies, n=2). Similarly, analyses by Wang et al. (2015)[71] and Zhan et al. (2015)[72] showed a significant dose–response relationship per 1–month increase in breastfeeding duration (RR 0.96, 95%CI 0.97–0.99 and RR 0.988 (CI not reported), respectively).

3.3.4 Parity

Evidence summary

Evidence classification: Convincing.

There is convincing evidence that parity is associated with a decreased risk of endometrial cancer and, conversely, that nulliparity is associated with an increased risk of endometrial cancer. The decreased risk for parity versus nulliparity is estimated to be 0.69 (95%CI 0.65–0.74)[73] and there is evidence of a dose–response relationship.

Background

Parity is defined as the number of times a female has been pregnant and carried the pregnancies to a viable gestational age. Nulliparity refers to never having completed a pregnancy to a viable gestational age.

Several plausible biological mechanisms for an association between parity and risk of endometrial have been proposed. Nulliparity may increase risk of endometrial cancer through the increased number of menstrual cycles associated with the absence of pregnancy and lactation, which leads to prolonged uninterrupted exposure to oestrogen. Elevated levels of oestrogens are known to stimulate proliferation of cells in the endometrium and promote cancer development.[74] In addition, at each birth delivery, there is mechanical shedding of malignant or premalignant endometrial cells as well as a shift in hormonal balance towards increased progesterone and reduced oestrogen levels, reducing cell proliferation and stimulating differentiation, which may influence the risk of endometrial cancer.[73]

Recent evidence

Five studies were identified for inclusion, four were pooled analyses[14, 66, 74, 75] and one was a meta–analysis[73]. Two pooled analyses[14, 74] were based on studies participating in the Epidemiology of Endometrial Cancer Consortium (E2C2)[vi], one[75] included four National Cancer Institute cohort studies from the US, and one[66] included six Australian cohort studies.

The meta-analysis by Wu et al. (2015)[73] included 42 observational studies and found a decreased risk for parous versus nulliparous women was 0.69 (95%CI 0.65–0.74; evidence of high heterogeneity). There was a non–linear dose-response relationship. Compared to nulliparity, having had 1, 2 or 3 births was associated with a decreased risk of endometrial cancer (RR 0.73, 95%CI 0.64–0.84; RR 0.62, 95%CI 0.53–0.74; and RR 0.68, 95%CI 0.65–0.70; respectively).[73]

The pooled analysis by Setiawan et al. (2013)[14] included 24 studies (10 cohort and 14 case–control studies) and showed that parity compared with nulliparity was associated with decreases in risk of type I endometrial cancer (OR 0.74 95%CI 0.68–0.81, OR 0.67 95%CI 0.63–0.72, OR 0.56 95%CI 0.52–0.60 and OR 0.40 95%CI 0.36–0.44; for 1, 2 , 3 and 4+ births, respectively). A similar finding was seen for type II endometrial cancer, with the OR ranging from 0.67 for 2 births to 0.54 for ≥4 births, compared to nulliparity. Analyses limited to women who had not used menopausal hormone therapy, and subgroup analyses based on study type and histology source, also showed similar negative associations between increasing parity and risk of type I and type II endometrial cancer.

The pooled analysis by Yang et al. (2015)[74] included 14 studies (2 cohort and 12 case–control studies) and reported that nulliparous women compared with parous women had an increased risk of endometrial cancer (OR 1.76, 95%CI 1.59–1.94), after adjustment for infertility. Relative to women who gave birth to three or more children, there were increased risks associated with having had fewer births (OR 1.21, 95%CI 1.12–1.31, OR 1.44, 95%CI 1.30–1.58, and OR 2.04, 95%CI 1.83–2.27; for 2 births, 1 birth, and no births, respectively).

The pooled analyses by Laaksonen et al. (2019)[66] and Schonfeld et al. (2013)[75] reported similarly increased risks of endometrial cancer among nulliparous women compared to parous women (HR 1.33, 95%CI 1.03–1.72; and HR 1.42, 95%CI 1.26–1.60, respectively).

3.3.5 Polycystic ovary syndrome (PCOS)

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between polycystic ovary syndrome (PCOS) and risk of endometrial cancer is inconclusive. A meta–analysis of a small number of case–control studies and a retrospective cohort study have indicated that PCOS may be associated with an increased risk of endometrial cancer, however the available studies have substantial

[vi] E2C2 is an international consortium formed in 2006 to provide a collaborative environment to address questions around endometrial cancer by pooling data from existing studies that would be underpowered in individual studies. To date, it includes data from more than 40 studies from the United States, Canada, Europe, Asia and Australia.

methodological limitations. High quality studies are required to confirm the nature of the association between PCOS and risk of endometrial cancer.

Background

PCOS is an endocrine disorder that affects around 8–13% of women of reproductive age and is characterised by features such as irregular or absent menstrual periods, difficulty getting pregnant, pelvic pain, skin and hair changes related to high levels of androgens such as hirsutism, and cysts on the ovaries.[76] The set of symptoms of PCOS are related to elevated male hormones in females.

PCOS is associated with factors that influence the risk of endometrial cancer such as obesity, diabetes, inflammation and metabolic syndrome. It is unclear whether any association with risk of endometrial cancer is due to individual risk factors (diabetes, obesity) or whether PCOS itself, with its specific metabolic features (such as hyperinsulinism, hyperglycaemia, insulin resistance, hyperandrogenism), increases the risk of cancer. Other factors, such as parity (nulliparous versus multi), age at first pregnancy and use/length of use of hormones (menopause hormone therapy, combined oral contraceptive), may act as confounders. PCOS may also increase risk of endometrial cancer via chronic anovulation with consequent increased oestrogen exposure unopposed by progesterone.[77]

Recent evidence

One meta–analysis[77] and one retrospective cohort study[78] were identified for inclusion.

The meta–analysis by Barry et al. (2014)[77] included five case–control studies involving 138 cases and 5,593 unmatched controls. Women with PCOS were 2.79 times more likely to have endometrial cancer compared to women without PCOS (OR 2.79, 95%CI 1.31–5.95). When the analysis excluded studies with women aged over 54 years, the increased risk of endometrial cancer for women with PCOS was higher (OR 4.05, 95%CI, 2.42–6.76). However the included studies were limited methodologically with use of unmatched controls, lack of adjustment for confounding factors, differences in the measurement and definition of PCOS, and likely high selection bias.

A population–based cohort study in Taiwanby Ding et al (2018)[78] included 8155 patients with PCOS and 32,620 matched patients without PCOS from the Taiwan National Health Insurance Research Database. A higher incidence of endometrial cancer was found in those women with PCOS compared to those women without PCOS (HR 17.7, 95%CI 4.9–64.2).[78] However the wide confidence interval indicates a lack of reliability in the findings, and the study was unable to account for major potential confounders such as smoking, Body Mass Index and family history of cancer.

3.4 Exogenous Hormones

3.4.1 Hormonal contraception—oral contraceptives

Evidence summary

Evidence classification: Convincing.

There is convincing evidence of an association between use of oral contraceptives[vii] and a decreased risk of endometrial cancer. The decreased risk for 'ever' versus 'never' use of oral contraceptives is estimated to be 0.69 (95%CI 0.66–0.73).[79] The risk decreases with increasing duration of use and persists for several decades after ceasing oral contraceptive use.

No pooled analyses, meta–analyses or cohort studies were identified examining an association between use of progestogen–only oral contraceptives and risk of endometrial cancer.

Use of combined oestrogen–progestogen oral contraceptives is estimated to have prevented 29.2% of endometrial cancers in Australia in 2013.[80]

Background

Combined oral contraceptives contain both oestrogen and progestogen. Progestogen–only contraceptives contain synthetic compounds designed to mimic some of the effects of natural progesterone. These compounds may be structurally related to progesterone or to testosterone. Combined oral contraceptives are the most commonly used contraceptive method while progestogen–only contraceptives are used by women who are breastfeeding or have other contraindications to oestrogen therapy (such as in the postpartum period.[81, 82]

The contraceptive action of combined oral contraceptives is mainly due to preventing ovulation by suppressing the levels of follicle stimulating hormone and luteinising hormone. Progestogen–only contraceptives achieve their contraceptive action by rendering the cervical mucus relatively impenetrable to sperm, and reducing the receptivity of the endometrium to implantation.[83] Combined oral contraceptives might protect against endometrial cancer by minimising unopposed oestrogen during the follicular phase of the menstrual cycle, thereby inhibiting oestrogen–induced cell proliferation.[79]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR 2018)[69] stated '*oral contraceptives, which contain either a combination of oestrogen and progesterone, or progesterone only, protect against endometrial cancer*'. Oral contraceptives are listed as an established protective factor for endometrial cancer.

[vii] More than 95% of oral contraceptive preparations used by women in studies were combined (oestrogen–progestogen) contraceptives (CGESEC 2015).

IARC

The International Agency for Research on Cancer (IARC 2012; Volume 100A)[84], based on data from cohort and case–control studies, concluded that combined oestrogen–progestogen oral contraceptives are: protective against cancer of the endometrium; that the magnitude of the protective effect increases with increasing duration of use; and, that it lasts for at least two decades after cessation of use. There is also evidence that the level of the protective effect is proportional to the progestogen potency of the preparation, and inversely proportional to its oestrogen potency.

For progestogen–only contraceptives, IARC (1999)[81] identified only one case–control study examining use of oral progestogen–only contraceptives, and one cohort and one case–control study assessing use of depot medroxyprogesterone acetate. IARC concluded that, 'although the evidence is based on small numbers of women, the results suggest that women who use progestogen–only contraceptives have a reduced risk for endometrial cancer'.

Recent evidence

Five studies were identified for inclusion, four were pooled analyses[14, 62, 66, 79] and one was a meta–analysis[85]. Setiawan et al. (2013)[14] and Cote et al. (2015)[62] included studies participating in the Epidemiology of Endometrial Cancer Consortium (E2C2[viii]).

The analysis by the Collaborative Group on Epidemiological Studies in Endometrial Cancer (CGESEC, 2015)[79] was based on 15 prospective studies; 11 retrospective studies with population controls and 10 retrospective studies with historical controls (N=143,019). More than 95% of oral contraceptive users in the studies [that reported on different formulations] used combined oral contraceptives. Only 56 cases had used progestogen–only oral contraceptives. Ever versus never use of oral contraceptives was significantly associated with a decreased risk of any endometrial cancer (RR 0.69, 95%CI 0.66–0.73), type I endometrial cancer (RR 0.68, 95%CI 0.65–0.71) and type II endometrial cancer (RR 0.75, 95%CI 0.66–0.85).[79]

A very similar magnitude of risk was reported in the pooled analyses by Setiawan et al. (2013)[14] and Laaksonen et al. (2019)[66]. Setiawan et al. (2013)[14] excluded women without an intact uterus from the control group and provided sensitivity analysis based on study type and source of histological classification. Among 10 cohort studies and 14 case–control studies, ever compared with never use of oral contraceptives was associated with a decreased risk of endometrial cancer (OR 0.73, 95%CI 0.69–0.77). Similarly, Laaksonen et al. (2019)[66], in a pooled analysis of six Australian cohort studies (n=160,555 women), reported a HR of 0.73 (95% CI 0.59–0.91) for ever compared with never use of oral contraceptives. A larger risk reduction was reported in the meta–analysis of seven studies (4 cohort and 3 case–control studies) by Gierisch et al. (2013)[85]; ever versus never use of oral contraceptives was associated with a decreased risk of endometrial cancer of OR 0.57 (95%CI 0.43–0.77).

[viii] E2C2 is an international consortium formed in 2006 to provide a collaborative environment to address questions around endometrial cancer by pooling data from existing studies that would be underpowered in individual studies. To date, it includes data from more than 40 studies from the United States, Canada, Europe, Asia and Australia.

A longer duration of use of oral contraceptives was reported to be associated with a larger reduction in risk of endometrial cancer in two pooled analyses. In the pooled analysis by CGESEC (2015)[79], the RR for every 5 years of oral contraceptive use was 0.76 (95%CI 0.73–0.78). This reduction in risk persisted for more than 30 years after ceasing oral contraceptive use. Similarly Cote et al. (2015)[62] reported a decreased risk of endometrial cancer in women who used oral contraceptives for 10+ years compared to never use (OR 0.49, 95%CI 0.27–0.88 and OR 0.69, 95%CI 0.58–0.83, in black women and white women, respectively). In the study by Laaksonen et al. (2019)[66], the protective effect of oral contraceptive use lasted for up to 30 years since ceasing use, irrespective of the duration of use, likely because women who used oral contraceptives for a shorter duration were more likely to have ceased longer ago.

3.4.2 Hormonal infertility treatment

Evidence summary

Evidence classification: Inconclusive.

The evidence regarding an association between use of fertility drugs and risk of endometrial cancer is inconclusive. The available studies are generally of poor quality. Any observed associations are likely due to underlying factors associated with the need for infertility treatment— such as ovulatory disorders and obesity—rather than the treatment itself.

Background

Medical treatment for subfertility principally involves the use of ovary–stimulating agents including 'stand alone' medications such as selective oestrogen receptor modulators (SERMs), e.g. clomiphene citrate; and as part of in vitro fertilisation (IVF) cycles including gonadotropins, gonadotropin–releasing hormone (GnRH) agonists and antagonists, and human chorionic gonadotropin.[86, 87]

Fertility drugs raise the serum levels of oestrogen and progesterone and gonadotropins and consequently increase the chance of multiple ovulations per menstrual cycle. It has been proposed that fertility drugs could increase risk of endometrial cancer as a result of prolonged exposure of the endometrium to unopposed or high levels of oestrogen, which in turn promotes mitotic activity and DNA replication errors and cancer development. However, by inducing ovulatory cycles and pregnancies, fertility drugs may also induce progesterone production, exerting potentially protective effects in terms of endometrial cancer risk.[87]

Recent evidence

Three meta–analyses[86-88] and one population study[89] were identified for inclusion.

A Cochrane review by Skalkidou et al. (2017)[87] included 19 studies (15 cohort and 4 case–control studies) examining the risk of endometrial cancer in women treated with ovary–stimulating drugs for subfertility. Overall, the quality of evidence was very low due to serious risk of bias and indirectness. Exposure to any ovary–stimulating drug was not associated with risk of endometrial cancer based on 6 studies without a general population control group (RR

0.96; 95%CI 0.67–1.37). Using a general population as the control group, meta–analysis of 15 studies indicated a positive association between use of any ovary–stimulating drug and risk of endometrial cancer (RR 1.75; 95%CI 1.18–2.61). Subgroup analyses revealed that clomiphene citrate and gonadotrophins used for subfertility were associated with an increased risk of endometrial cancer (RR 1.32; 95%CI 1.01–1.71; 5 studies, RR 1.55; 95%CI 1.03–2.34; 4 studies, respectively) but gonadotropin–releasing hormone was not (RR 1.21; 95%CI 0.65–2.27; 2 studies). The association between clomiphene and risk of endometrial cancer appeared to be driven by effects observed with high doses of clomiphene (RR 1.69; 95%CI 1.07–2.68), high number of cycles (RR 1.69; 95%CI 1.16–2.47) and in studies with long follow–up durations for >10 years (RR 1.35; 95%CI 1.03–1.78). This may largely be due to underlying risk factors in women, such as polycystic ovarian disease and obesity, who need treatment with clomiphene, rather than exposure to the treatment itself.

Saso et al. (2015)[86] examined comparative retrospective studies of 'fertility treatment', used either as an independent therapy or as part of IVF cycles, versus 'non–fertility treatment' and reporting the incidence of uterine cancer (including mainly endometrial carcinoma and the less common uterine sarcoma)as an outcome. Incidence of uterine cancer in the fertility treatment group was not significantly different to the non–fertility treatment group (OR 0.78; 95%CI, 0.39–1.57; 6 studies; high heterogeneity). Sub–group analyses with use of different drugs also showed no significant associations while meta–analysis of two studies in which fertility drugs were administered only as part of IVF treatment showed a significant decreased risk of uterine cancer compared to not using them at all (OR 0.38, 95%CI 0.30–0.47).

Siristatidis et al. (2013)[88] did not find an association between controlled ovarian hyperstimulation for IVF and risk of endometrial cancer in nine cohort studies analysed with infertile women as the reference group (RR 0.45; 95%CI 0.18–1.14). Using the general population as the reference group resulted in a significant positive association between IVF and risk of endometrial cancer (RR 2.04; 95%CI 1.22–3.43). The authors concluded that IVF does not seem to be associated with increased endometrial cancer risk when the confounding effect of infertility is neutralised.

A large recent population based study by Williams et al. (2018)[89] assessed 255,786 women who had assisted reproduction in Great Britain, 1991–2010, as recorded by the Human Fertilisation and Embryology Authority, and risk of cancer of the corpus uteri. Over 92% of corpus uteri tumours were epithelial. Assisted reproduction was not associated with incidence of cancer of the corpus uteri compared with the general population (standardised incidence ratio [SIR] 1.12; 95%CI 0.95–1.30). Number of cycles, age at first treatment and duration since treatment completion did not influence the risk of cancer of the corpus uteri. A significantly increased risk of cancer of the corpus uteri was observed in women who had assisted reproduction and had an ovulatory disorder (SIR 1.59, 95%CI 1.13–2.17).[89]

3.4.3 Intrauterine device (IUD) contraception

Evidence summary

Evidence classification: Suggestive—hormonal IUDs; inert IUDs.

Evidence classification: Inconclusive—copper IUDs.

The evidence is suggestive of an inverse association between use of hormonal (levonorgestrel–releasing) IUDs or inert IUDs and risk of endometrial cancer. One large cohort study[90] and a much smaller cohort study[91] indicate that use of hormonal IUDs are associated with a decreased risk of endometrial cancer. A pooled analysis has shown that ever use versus never use of inert IUDs is associated with a decreased risk of endometrial cancer. There is no evidence of an association between use of copper IUDs and risk of endometrial cancer.

Background

IUD is a form of long–term, reversible contraception which is placed in the uterine cavity. The two types available in Australia are the copper IUD (made of plastic and copper), designed to stay in place for up to 10 years (Multiload lasts for up to five years and the Copper T for up to 10 years), and the hormonal IUD (Mirena™), for five years. Hormonal IUDs are made of plastic and contain a synthetic progesterone. Inert IUDs do not have a bioactive component, are less effective than copper or hormonal IUDs, and are not used in Australia.

IUDs evoke foreign body responses inducing secretion of macrophages, neutrohpils and lymphocytes. The inflammatory environment is believed to inhibit pre–fertilisation factors such as sperm migration and viability, and post–fertilisation factors including implantation prevention and damage to early embryo. Hormonal IUDs also make the mucus in the cervix thicker thereby blocking sperm, suppress growth of the endometrial lining resulting in a thin endometrium making it harder for an egg to attach, and sometimes stops ovulation.

Proposed mechanisms for IUDs being associated with a decreased risk of endometrial cancer include: increased decidual loss, alterations in hormone receptor expression, and stimulation of an inflammatory microenvironment in the uterus.[92] It is unclear whether IUDs might lower endometrial cancer risk through hormonal mechanisms; studies have provided conflicting evidence regarding variations in serum ovarian steroid–hormone levels between IUD users and non–users.

Recent evidence

A pooled analysis of individual patient data from 18 studies (4 cohort and 14 case–control studies; 8,801 cases and 15,357 controls) by Felix et al (2015)[92] was identified. Ever versus never use of IUDs (any sort) was associated with a decreased risk of endometrial cancer (OR 0.81, 95%CI 0.74–0.90), although the finding was significant for case–control but not cohort studies (OR 0.82, 95%CI 0.69–0.98; OR 0.86, 95%CI 0.67–1.10, respectively). The inverse association was strongest among users of inert IUDs (OR 0.69, 95%CI 0.58–0.82). In contrast, no association was observed among users of copper IUDs (OR 0.89, 95%CI 0.66–1.21), hormone–releasing IUDs (OR 0.97, 95%CI 0.44–2.14), or use of a combination of IUDs (OR 0.88, 95%CI 0.65–1.19). The authors noted that only 21 cases and 12 controls were exposed to the hormone–releasing IUDs, and thus a meaningful estimate for this device was not possible. They also noted that 'more studies are needed to investigate a possible association given the inverse association for levonorgestrel–releasing IUD and endometrial cancer risk demonstrated by a Finnish study' (Soini et al. 2014)[91].

More recent data reported by Jareid et al (2018)[90] from a cohort study of 104,318 women in the Norwegian Women and Cancer Study (NOWAC), are consistent with the findings by Soini

et al. (2014)[91]. A substantially decreased risk of endometrial cancer was observed among women who had ever used a levonorgestrel–releasing IUD (9,144 women) compared to 95,174 never users (RR 0.22, 95%CI 0.13–0.40).

The analysis by Felix et al. (2015)[92] showed that compared with never use of IUD, older age at first use (≥35 years OR 0.53, 95%CI 0.43–0.67), older age at last use (≥45 years OR 0.60, 95%CI 0.50–0.72), longer duration (≥10 years OR 0.61, 95%CI 0.52–0.71), and recent use (within 1 year of study entry OR 0.39, 95%CI 0.30–0.49) were inversely related to endometrial cancer risk. Moreover, the association between IUD use and endometrial cancer risk was significantly modified by parity, menopausal status and menopause hormone therapy (MHT) use. Nulliparous IUD users (OR 0.48, 95%CI 0.34–0.68) had a more pronounced decreased risk of endometrial cancer than parous IUD users (OR 0.63, 95%CI 0.54–0.74). IUD use was associated with a decreased risk of endometrial cancer among MHT users compared to non–users, which may indicate that IUDs exert an anti–hormonal influence; however, the type and duration of MHT use was unknown in this analysis therefore this inference is uncertain.

3.4.4 Menopausal hormone therapy/Hormone replacement therapy

Evidence summary

Oestrogen–only menopausal hormone therapy (MHT)

- Evidence classification: Convincing (oral or transdermal oestrogen–only MHT).
- Evidence classification: Inconclusive (vaginal oestrogen–only MHT).

Combined oestrogen–progestogen MHT

- Evidence classification: Convincing (cyclical oestrogen–progestogen MHT (progestogen <10 days/month)).
- Evidence classification: Inconclusive (cyclical oestrogen–progestogen MHT (progestogen ≥10 days/month).
- Evidence classification: Suggestive (continuous combined oestrogen–progestogen MHT).

Tibolone

- Evidence classification: Probable (tibolone).

There is convincing evidence that use of oral or transdermal oestrogen–only menopausal hormone therapy (MHT), also known as 'hormone replacement therapy (HRT)', is associated with an increased risk of endometrial cancer. The evidence is consistent across a large number of studies. The increased risk associated with 'ever use' versus 'never use' of oestrogen–only MHT has been estimated as 2.3 (95%CI 2.1–2.5).[93] Risk increases with increasing duration of use and the increased risk decreases with time since last use, but probably persists for at least 10 years post–use.

The evidence for an association between use of vaginal oestrogen–only MHT and risk of endometrial cancer is inconclusive. A limited number of studies have shown inconsistent findings.

There is convincing evidence that use of cyclical (sequential) combined MHT involving fewer than 10 days of progestogen per month is associated with an increased risk of endometrial cancer. This risk has been estimated in a meta–analysis to be 1.76 (95%CI 1.51–2.05).[94]

The evidence for an association between use of cyclical combined MHT involving more than or equal to 10 days of progestogen per month is inconclusive. Although one meta–analysis showed no association across eight studies, findings were inconsistent across studies and data on effect of duration of use are limited. Any association may be modified by body mass.

The evidence is suggestive of an association between use of continuous combined oestrogen–progestogen MHT and decreased risk of endometrial cancer. One meta–analysis of a large number of studies has shown a decreased risk however findings across individual studies are mixed, and there are mixed findings in relation to duration of use.

Use of tibolone is probably associated with an increased risk of endometrial cancer. The evidence is consistent across a limited number of recent cohort studies and one recent cohort study showed that risk increases with increasing duration of use.[95] Risk estimates have varied from around two to nearly four times increased risk.

It is estimated that 3.1% of endometrial cancers in Australia in 2010 were attributable to the current use of oestrogen–only MHT.[96]

Background

Menopausal hormone therapy (MHT), also known as 'hormone replacement therapy(HRT)', is used to mitigate the effects of diminishing oestrogen in perimenopausal or menopausal women. Oestrogen–only MHT refers to the administration of an oestrogen without a progestogen. In the 1970s it was shown that oestrogen–only therapy was associated with an increased risk of endometrial cancer; progestogens were added to mitigate this risk. Thus, oestrogen–only MHT is mainly prescribed to women who have had a hysterectomy.[84] Combined MHT involves the co–administration of an oestrogen and a progestogen. Progestogens are provided either continuously (>25 days/month), or sequentially (<25 days/month) including cyclically (10–14 days/month). Tibolone is a synthetic progestogenic hormone which, once metabolised, acts like oestrogen, progestogen, and testosterone.

Use of oestrogen–only and cyclic oestrogen plus progestogen MHT exposes the endometrium to unopposed oestrogen, which is a risk factor associated with the development of endometrial cancer.[97]

The increased risk of endometrial cancer associated with tibolone is thought to be due to the drug being more oestrogenic and/or less progestogenic with regard to the endometrium.[98]

IARC

The International Agency for Research on Cancer (IARC 2012, Volume 100 A)[84] concluded that oestrogen–only menopausal therapy causes cancer of the endometrium. The Monograph indicates that an earlier IARC Monograph (2007, Volume 91)[83] summarised data from three cohort studies and over 30 case–control studies, and noted consistent findings of an increased risk. Risk increased with increasing duration of use, and decreased with time

since last use, but the risk remained elevated for at least 10 years after stopping treatment. The risk is also increased for atypical endometrial hyperplasia, a presumed precursor of endometrial cancer.

Findings from four additional cohort studies and five case–control studies contained in the updated Monograph supported the earlier findings. There is consistent evidence that the risk of endometrial cancer is increased in women taking unopposed oestrogen, and the increased risk remains evident when the opposing progesterone is taken for fewer than 15 days per month.[84] The increased risk decreases with the number of days per month that progestogens are added to the regimen. At the time of publication, IARC (2012)[84] stated it is not known whether continuous use (or daily use) reduces the risk of endometrial cancer compared to baseline.

Recent evidence

One meta–analysis by Grady et al. (1995)[93] and and one cohort study by Karageorgi et al. (2010)[65] was included for oestrogen–only MHT. One meta–analysis by Brinton & Felix (2014)[94] and four prospective cohort studies[95, 97, 99, 100] were identified for inclusion for other types of MHT.

A meta–analysis by Grady et al (1995)[93] showed that 'ever use' versus 'never use' of oestrogen–only MHT was associated with an increased risk of endometrial cancer (RR 2.3, 95%CI 2.1–2.5; 29 studies). The estimated risk was lower in the four cohort studies compared to the 25 case–control studies (RR 1.7, 95%CI 1.3–2.1 and RR 2.4, 95%CI 2.2–2.6, respectively). Risk increased with increasing duration of use (RR 1.4, 95%CI 1.0–1.4, RR 2.8, 95%CI 2.3–3.5, RR 5.9, 95%CI 4.7–7.5, and RR 9.5, 95%CI 7.4–12.3; for duration of use of <1, 1–5, 5–10, and >10 years, respectively). Some of the increased risk associated with long duration of use may reflect the fact that women who started taking oestrogen many years ago were more likely to be treated with higher doses than currently used. Two of the included studies provided risk estimates stratified by duration and dose, indicating increased risks of 4.8 and 4.3 for at least 5 years use of oestrogen–only MHT at current doses (≤0.625 mg of conjugated oestrogen).

Karageogi et al. (2010)[65] analysed data from the Nurses' Health Study, a large prospective cohort study with 778 cases of endometrial adenocarcinoma, and showed that the increased risk among current users of oestrogen–only MHT for <5 years and for ≥5 years was 2.46 (95%CI 1.56–4.06) and 10.78 (95%CI 7.53–15.44), respectively, compared to never users. This risk estimate was used by Jordan et al. (2015)[96] to calculate the population attributable fraction of endometrial cancer attributable to oestrogen–only MHT in Australia in 2010.

Brinton & Felix (2014)[94] conducted a meta–analysis of five cohort studies and nine case–control studies and showed that use of continuous (>25 days/month) combined oestrogen–progestogen MHT was associated with a decreased risk of endometrial cancer (OR 0.78, 95%CI 0.72–0.86) with similar risk estimates for sub–group analysis by study type. Included individual studies varied in findings, with results ranging from no association, to increased risk and to modest decreased risks. More recent studies with larger sample sizes and greater statistical power to detect effects have mainly shown decreased risks. Brinton & Felix (2014)[94] also reported on the statistically insignificant decreased risk observed in two randomised controlled trials, the Women's Health Initiative and the Heart and Estrogen/Progestin Therapy trial. The findings from both RCTs were limited by small number of cases and short exposure durations. There have been mixed findings from cohort studies regarding duration of use of

continuous combined MHT. Larger protective effects are observed among women with a high Body Mass Index (BMI).

Brinton & Felix (2014)[94] report on the meta–analysis by Beral et al. (2005)[101] which indicated an overall RR of 1.14 (95%CI 1.01–1.28) associated with use of sequential (cyclical) combined MHT. A meta–analysis examining use of sequential combined MHT involving progestogen on fewer than 10 days/month by Brinton & Felix (2014)[94] provided an overall RR of 1.76 (95%CI 1.51–2.05; 7 case–control and 4 cohort studies). However there was no association when the sequential combined MHT involved ≥10 days of progestogen/month (overall RR 1.07, 95%CI 0.92–1.24; 6 case–control studies and 2 cohort studies). It was noted that increased risks associated with use of sequential combined MHT have been shown to occur among thin women in several cohort studies. It was further noted that data are currently limited as to whether risk remains non–elevated when long–duration use of the regimen is involved.

Mørch et al. (2016)[97] analysed data from the Danish Sex Hormone Register Study (n=914,595 women). 'Ever' versus 'never' use of oestrogen–only MHT was associated with an increased risk of endometrial cancer (RR 2.70, 95%CI 2.41–3.02), regardless of route of administration (oral, transdermal or vaginal). Associations were less strong and non–significant for sub–group analyses for type II compared to Type 1 cancers (RR 1.43, 95%CI 0.85–2.41 and 2.95, 95%CI 2.61–3.33). Use of cyclic combined MHT was associated with an increased risk of endometrial cancer (RR 2.06, 95%CI 1.88–2.27) while use of continuous combined MHT was not associated with risk of endometrial cancer (RR 1.02, 95%CI 0.87–1.20). The risk of type II endometrial cancer was decreased in some analyses, for example use of continuous combined MHT compared with never use was associated with a decreased risk of 0.45 (95%CI 0.20–1.01).

In an analysis of data from the E3N French cohort study (n=65,630 postmenopausal women), Fournier et al. (2014)[99] showed that ever versus never use of oestrogen–only MHT was associated with increased risk of endometrial cancer (HR 1.80, 95%CI 1.31–2.49). Risk increased with increasing duration of use – compared with never use, ≤ 5 years' use with HR 1.81 (95%CI 1.27–2.58) and >5 years' use was associated with HR 3.53 (95%CI 1.44–8.66). Use of oestrogen plus micronized progesterone was also associated with an increased risk of endometrial cancer (1.80, 95%CI 1.38–2.34; 1.39, 95%CI 0.99–1.97; 2.66, 95%CI 1.87–3.77; for ever, duration ≤5 years and duration ≥5 years, compared to never use, respectively) but use of other progesterone or norsteroid derivatives in combination with oestrogen was not associated with risk of endometrial cancer, except for longer–term use (>5 years) of oestrogen plus dydrogesterone (HR 1.69, 95%CI 1.06–2.70).

Using data from participants of the Women's Health Initiative (WHI) observational study, Crandall et al. (2018)[100] showed that 'ever' versus 'never' use of vaginal oestrogen–only MHT was not associated with risk of endometrial cancer (HR 1.47, 95%CI 0.75–2.90).

Two recent cohort studies reported on the association of tibolone, a synthetic steroid MHT with estrogenic, progestagenic and androgenic properties, and risk of endometrial cancer.[95, 97] Mørch et al. (2016)[97] showed that tibolone is associated with an increased risk of endometrial cancer in ever users compared with never users (RR 3.56, 95%CI 2.94–4.32). Løkkegaard and Mørch (2018)[95] extended the analysis of the Danish Sex Hormone Register Study to show that risk of endometrial cancer was increased with longer duration of tibolone use (Incidence Rate Ratio (IRR) for <2 years: 3.00, 95%CI 1.70–5.31, IRR for 2–4 years: 3.31, 95%CI 2.21–4.95; IRR for 5–9 years: 3.77, 95%CI 2.81–5.05; IRR for 10+ years: 3.80, 95%CI 2.56–5.64). These findings were indicated to support those of the UK Million Women Study reported by Beral et al. (2005)[101] (RR 1.79, 95%CI 1.43–2.25).

3.5 Lifestyle factors

3.5.1 Alcohol consumption

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between alcohol consumption and risk of endometrial cancer is inconclusive. Several recent meta–analyses of cohort and case–control studies have shown no difference in risk of endometrial cancer among women with high versus low intakes of alcohol consumption; and there is no evidence of a dose–response relationship.

Background

Several biological mechanisms have been proposed for an association between alcohol consumption and risk of endometrial cancer. Alcohol has been shown to increase the levels of oestrogen, which is a well–accepted driver of endometrial carcinogenesis. Prolonged exposure to estrogen leads to increased DNA replication errors and somatic mutations, which can lead to a malignant phenotype.[102] Alcohol intake has also been associated with enhanced insulin sensitivity and reduced fasting insulin concentrations. Insulin can stimulate the proliferation of endometrial cells by binding to insulin receptors in the endometrium and by increasing circulating free insulin–like growth factor–1 through decreasing the levels of insulin–like growth factor–binding protein–1. A protective effect for alcohol on endometrial cancer risk is thus also plausible. The counteracting mechanisms may therefore attenuate any association between alcohol consumption and endometrial cancer risk.[102]

IARC

For endometrial cancer specifically, the International Agency for Research on Cancer (IARC 2012, Volume 100E)[103] concluded that the evidence for an association between consumption of alcoholic beverages and risk of cancer of the endometrium is inconsistent. The majority of studies show no association; the few that show an inverse association were not able to adjust for tobacco smoking. Among both the cohort and case–control studies, there was no consistent evidence of an interaction between consumption of alcoholic beverages and different variables known or suspected to be associated with cancer of the endometrium, such as the use of menopause hormone therapy, body size, age, tobacco smoking, parity, education, physical activity, energy intake and other dietary aspects, and oral contraceptive use.

Although the evidence for endometrial cancer was considered inconsistent, IARC concluded that alcohol consumption is '*carcinogenic to humans (Group 1)*' and that there is '*sufficient evidence in humans for the carcinogenicity of alcohol consumption*' for cancers of the oral cavity, pharynx, larynx, oesophagus, colon and rectum, liver and breast.

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR 2018)[69] judged the evidence for the association between alcohol intake and risk of endometrial cancer to be 'Limited – no conclusion', based on the systematic review of evidence to December 2012 (CUP Endometrial SLR)[23].

A dose–response meta–analysis for alcohol consumption based on nine prospective cohort studies showed no significant association between risk of endometrial cancer per 10g alcohol intake per day (RR 1.01, 95%CI 0.97–1.06)(CUP Endometrial SLR).[23] Only one study showed a positive association between alcohol consumption and risk of endometrial cancer.

Recent evidence

Four studies were identified for inclusion, one was a pooled analysis (of only three case–control studies)[104] and three were meta–analyses[102, 105, 106].

The meta–analysis by Si et al. (2017)[105] reported no difference in risk of endometrial cancer between women in the highest versus the lowest category of alcohol–drinking pattern (OR 0.98, 95%CI 0.73–1.30; 5 cohort and 3 case–control studies).

Zhou et al. (2017)[102] included ten cohort studies (9766 cases and 1,612,798 participants), including the five cohort studies that were included in the meta–analysis by Si et al. (2017)[105]. Zhou et al (2017)[102] similarly found no difference in risk of endometrial cancer between women in the highest compared to lowest categories of alcohol consumption (RR 1.04, 95%CI 0.88–1.22). Subgroup analyses showed no differences in risk, including when limited to studies that adjusted for all the major confounders (Body mass index, smoking, oral contraceptive use and menopause hormone therapy), nor across different alcohol types. The RRs for alcohol intake from wine, beer, and liquor were 1.10 (95%CI 0.80–1.51), 0.94 (95%CI 0.72–1.22), and 1.04 (95%CI 0.86–1.27), respectively. In the dose–response analysis, there was no significant association between daily alcohol consumption and risk of endometrial cancer (RR per 1 drink (12g alcohol) 1.00, 95%CI 0.80–1.51).

When comparing categories of alcohol intake and risk of endometrial cancer the evidence is inconsistent. For example, in a meta–analysis by Bagnardi et al. (2015)[106] based on results from 21 observational studies (8 cohort and 13 case–control studies), no significant association with endometrial cancer risk was found in women with moderate intake (≤ 50 g per day) or light intake (≤12.5 g per day) compared to no alcohol intake (RR 0.97, 95%CI 0.92–1.01, and RR 0.99, 95%CI 0.84–1.16, respectively). Conversely, a pooled analysis of data from three case–control studies not included in any of the three meta–analyses] adjusted for major confounders including smoking [in Italy by Filomeno et al. (2015)[104], showed a decreased risk of endometrial cancer associated with moderate alcohol intake versus low or high alcohol intake (OR 0.76, 95%CI 0.65–0.87). Further, the most recently published data from the long–term, prospective Nurses' Health Study by Je et al. (2014)[107] [the only additional study to the meta–analysis by WCRF/AICR (2012)[23] that was included in the two most recent meta–analyses] showed a decreased risk of endometrial cancer for light alcohol consumption. Women with an alcohol intake of less than 5 g per day (approximately half a drink per day) had a 22% lower risk of endometrial cancer than non–drinkers (RR 0.78, 95%CI 0.66–0.94); however higher levels of daily alcohol consumption were not associated with risk of endometrial cancer.

3.5.2 Body fatness

Evidence summary

Evidence classification: Convincing.

There is convincing evidence of an association between body fatness (as reflected by Body Mass Index (BMI), waist circumference, and weight gain) and an increased risk of endometrial cancer.

There is a dose–response relationship—the increased risk of endometrial cancer per 5 BMI units (kg/m^2) is estimated to be 1.54 (95%CI 1.47–1.61)—however the dose–response relationship is non–linear, with a steeper increase in risk at higher BMI levels.[108] For example, having a BMI of 30 kg/m^2, 35 kg/m^2 and 40 kg/m^2 is associated with approximately 2, 5 and 10 times the risk of endometrial cancer as having a BMI of 20–22 kg/m^2 (normal weight).[108]

The increased risks associated with other measures of body fatness have been estimated to be 1.18 (95%CI 1.14–1.23) per 5 kg weight gain after early adulthood and 1.27 (95%CI 1.17–1.39) per 10 cm increase in waist circumference.[108]

It is estimated that 26.4% of endometrial cancers in Australia in 2010 were attributable to overweight/obesity, and that 24.2%–36.0% of endometrial cancer cases could be avoided during 2013–2037 if overweight and obesity were eliminated in the Australian population.[109,110] It has also been estimated that 41.9% (95%CI 32.3%–50.1%) of endometrial cancers in Australia during 2017–2026 will be attributable to overweight and obesity, with obesity alone explaining 34.5% (95%CI 27.5%–40.9%) of the cases.[66]

Background

Body fatness is reflected by Body Mass Index (BMI), and includes measures of abdominal adiposity such as weight circumference and waist–to–hip ratio. BMI is measured in units of weight and height (kg/m^2) and categories of BMI are: Underweight <18.5; normal weight (healthy weight) 18.5–24.9; overweight 25–29.9; and, obese ≥30 kg/m^2. Categories of obesity are sometimes included: obese class 1 30–34.9, obese class 2 (severe obesity) 35–39.9, and obese class 3 (morbid obesity) ≥40 kg/m^2.

Body fatness may be associated with an increased risk of endometrial cancer through a number of mechanisms. Elevated levels of hormones such as oestrogen associated with obesity can promote cancer development. Obesity is associated with lower levels of sex hormone binding globulin (SHBG), a protein that binds and opposes the biologic activity of circulating oestrogen.[14] In postmenopausal women, oestrogen synthesis is increased due to aromatase activity in adipose tissue.[69]

Obesity is also associated with a low–grade chronic inflammatory state which can promote cancer development. Obese individuals have elevated levels of circulating tumour necrosis factor (TNF)–alpha, interleukin–6, C–reactive protein and leptin compared with lean people. Pro–inflammatory factors are produced by adipocytes and infiltrating macrophages. In addition, hyperinsulinaemia and insulin resistance, particularly caused by abdominal fatness, can promote growth of cancer cells and increase risk of endometrial cancer.[69]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR 2018)[69] judged the evidence for the association between adult body fatness and increased risk of endometrial cancer to be 'Strong–convincing', based on the systematic review of evidence to December 2012 (CUP Endometrial cancer SLR)[23].

WCRF/AICR (2018)[69] considered BMI, measures of abdominal adiposity and adult weight gain as indicating interrelated aspects of body fatness and fat distribution. The evidence for abdominal fatness and weight gain was considered to be less robust than that where BMI was used as the measure of body fatness. However, abdominal fatness and weight gain supported the evidence for an association between overall body fatness and endometrial cancer risk. Any change in weight was interpreted to better reflect fatness than adult weight itself given that increases in body weight during adulthood depend on accumulation of fat more than lean tissue.

Twenty six studies contributed to the dose–response meta–analysis for BMI and risk of endometrial cancer. The summary RR per 5 BMI units was 1.50 (95%CI 1.42–1.59) with evidence of high heterogeneity, which was due to differences in the size of the effect. There was evidence of a non–linear dose–response relationship, with a steeper increase in risk at higher BMI levels. For example, having a BMI of 30 kg/m^2, 35 kg/m^2 and 40 kg/m^2 is associated with approximately 2, 5 and 10 times the risk of endometrial cancer as having a BMI of 20–22 kg/m^2 (normal weight) (risks approximated from Figure 84, CUP Endometrial SLR)[23].

In subgroup analysis by menopausal status, a significantly increased risk was observed for premenopausal women and postmenopausal women (RR 1.41, 95%CI 1.37–1.45 and 1.54, 95%CI 1.39–1.71; respectively). In subgroup analysis by menopausal hormone therapy (MHT) use, a significant increased risk of endometrial cancer was observed for those who used MHT and those who have never used MHT, although the effect was stronger in those who had never used MHT (RR 1.15, 95%CI 1.06–1.25 and RR 1.73, 95%CI 1.44–2.08; respectively).

A dose–response meta–analysis for weight change based on five studies showed a 16% increase in endometrial cancer risk per 5 kg weight gain after early adulthood (RR 1.16; 95%CI 1.10–1.22; evidence of high heterogeneity due to differences in the size but not the direction of the effect). A dose–response meta–analysis for waist circumference based on 4 cohort studies showed a 13% increase in endometrial cancer risk per 5 cm increase in waist circumference (RR 1.13; 95%CI 1.08–1.18; evidence of high heterogeneity due to differences in the size but not the direction of the effect). A dose–response meta–analysis for waist–hip ratio based on 5 studies found a 21% increase in endometrial cancer risk per 0.1 units (RR 1.21, 95%CI 1.13–1.29; with no evidence of heterogeneity).

Recent evidence

A systematic review and meta–analysis by Aune et al. (2015)[111] was conducted as part of the WCRF Continuous Update Project and included a number of different weight–related measures. Across 32 prospective cohort studies (published up to February 2015):

- The risk of endometrial cancer per 5–unit increase in BMI (kg/m^2) was estimated to be RR 1.54 (95%CI 1.47–1.61; 30 studies). As per the earlier analysis for the CUP Endometrial SLR (2012)[23], there was evidence of non–linearity in the BMI relationship such that risk

increased more noticeably over 25 kg/m^2. Having a BMI of 30 kg/m^2, 35 kg/m^2 and 40 kg/m^2 is associated with approximately 2, 5 and 10 times the risk of endometrial cancer, respectively, as having a BMI of 20 kg/m^2 (approximated from Figure 1B). Some increase in risk was observed even within the normal BMI range, with the lowest risk at around BMI 20 kg/m^2.

- There was evidence of effect modification by hormone replacement therapy use, with a stronger association among never users compared with ever users (summary RRs of 1.65 (95%CI 1.33–2.05) and 1.10 (95%CI 1.06–1.14), respectively). This finding is attributed to the effect of additional exogenous hormones being diminished among women that already have high levels of circulating oestrogens due to high body fatness.
- Nine studies were included in the analysis of BMI at 18–25 years and the summary RR per 5–units increase was 1.45 (95%CI 1.28–1.64), with an approximately linear association from a BMI of 20 kg/m^2.
- For weight, an analysis of eight studies showed a non–linear increase in risk of endometrial cancer per 5 kg in weight of 1.18 (95%CI 1.14–1.23; 8 studies). As for BMI across adulthood, the curve was steeper at higher levels of weight.
- For weight gain between age 18–20 years and baseline, the increased risk of endometrial cancer per 5 kg increase in weight gain was estimated to be 1.18 (95%CI 1.15–1.21), across four studies adjusted for BMI or weight in young adulthood. This association was largely linear and was clearer for weight gain of over 10 kg.
- Each 10 cm increase in WC was associated with an increased risk of endometrial cancer of RR 1.27 (95%CI 1.17–1.39; 4 studies) and there was evidence of non–linearity in the relationship, with a steeper increase in risk at higher levels of waist circumference.
- Each 0.1–unit increase in WHR was associated with an increased risk of endometrial cancer of RR 1.21(95%CI 1.13–1.29; 5 studies). However, when the analysis was restricted to the 3 studies which adjusted for BMI, there was no statistically significant association (RR 1.07, 95%CI 0.97–1.17).

A pooled analysis of individual patient data (IPD) by Setiawan et al. (2013)[14] excluded women without an intact uterus from the control group and provided sensitivity analysis based on study type and source of histological classification. Twenty–four studies (10 cohort and 14 case–control studies) were included in the analysis and there was a significant association between body fatness and increased risk of endometrial cancer. Compared with being normal weight or underweight, the increased odds of Type 1 endometrial cancer ranged from 1.45 to 7.14 for increasing categories of overweight and obesity, and the increased odds of type II endometrial cancer ranged from 1.16 to 3.11 for increasing categories of overweight and obesity. The increased odds per 2–unit increase in BMI (kg/m^2) were estimated as OR 1.20 (95%CI 1.19–1.21) and OR 1.12 (95%CI 1.09–1.14) for type I and type II endometrial cancer, respectively.

In a recent pooled analysis of six Australian cohort studies, the risk of endometrial cancer was 3.17 (95% CI 2.52–3.98) and 1.44 (95% CI 1.13–1.83) in obese and overweight women, respectively, compared with women of normal weight.[66] The HR per 5–unit increase in BMI was 1.61 (95%CI 1.54–1.76).

Similar findings for BMI and risk of endometrial cancer were reported across other recent pooled– and meta–analyses. For example, compared to normal weight women, overweight women had a significantly increased risk of endometrial cancer (RR 1.32, 95%CI 1.16–1.50; RR

1.37, 95%CI 1.18–1.60; RR 1.34, 95%CI 1.20–1.48) as reported by Zhang et al. (2014)[112], Rota et al. (2016)[113] and Jenabi et al. (2015)[114], respectively. Rota et al. (2016)[113] determined the increased risk of endometrial cancer per 5–unit increase in BMI (kg/m^2) to be RR 1.63 (95%CI 1.52–1.75).

A recent analysis of data from the Norwegian Women and Cancer (NOWAC) cohort study by da Silva et al. (2018)[115] showed an over two–fold increase in risk of endometrial cancer among obese women compared with women of normal weight (HR 2.78, 95%CI 2.30–3.35). Overweight was also associated with increased risk (HR 1.45, 95%CI 1.24–1.68). There were no significant interactions between MHT use and BMI, although menopausal status modified the effect of BMI in relation to endometrial cancer risk, with a statistically significant interaction between perimenopausal status and obesity. Weight gain was also associated with an increased risk of endometrial cancer (HR 1.27, 95%CI 1.01–1.61 and HR 1.40, 95%CI 1.04–1.88; for moderate weight gain (5–10 kg) and high weight gain (≥10 kg), respectively). There was a clear dose–response relationship (HR per 5 kg weight gain = 1.12, 95%CI 1.04–1.20).

Barberio et al. (2019)[116] analysed data from 26,607 participants in the Alberta's Tomorrow Project prospective cohort study to examine whether overall body shape and size as measured by BMI, or central body fatness as measured by WC and WHR, is the stronger predictor of cancer risk and to examine the associations between various measures of body shape and size and the risk of all–cancer and site–specific cancers. There was strong evidence of an increased risk for all three anthropometric measures (BMI, WC, and WHR). The positive association between a BMI ≥30 kg/m^2 and the risk of endometrial cancer (HR 4.52, 95%CI 2.69–7.61) was slightly attenuated adjusted for waist circumference (HR 3.12, 95%CI 1.43–6.81). Similarly, the positive association between a waist circumference of ≥88 cm and the risk of endometrial cancer (HR 3.14, 95%CI 2.04–4.85) remained significant in models that adjusted for all covariates and BMI (HR 2.41, 95%CI 1.38–4.22), indicating that WC may be a stronger predictor of endometrial cancer risk than BMI. For WHR, an increased risk of endometrial cancer was observed for women in the highest versus lowest quartile of WHR (HR 4.19, 95%CI 2.42–7.23), however in a final model adjusted for BMI, the increased risk was no longer observed (HR 1.29, 95%CI 0.47–3.49).

Arthur et al. (2019)[117] examined the association between metabolic syndrome, with and without inclusion of WC in the definition, and risk of endometrial cancer among 24,210 women participating in the Women's Health Initiative prospective cohort study. Metabolic syndrome was considered a constellation of risk factors including obesity, hypertension, insulin resistance, and dyslipidemia. Metabolic syndrome – including WC – was associated with increased risk of endometrial cancer (HR 2.27, 95%CI 1.67–3.09). The association remained positive, but was no longer statistically significant after excluding WC from the definition (HR 1.34, 95%CI 0.97–1.84).

3.5.3 Coffee and tea

Evidence summary

Evidence classification—coffee: Probable.

Evidence classification—green tea: Suggestive.

Evidence classification—black tea: Inconclusive.

Coffee (independent of caffeine) is probably associated with a decreased risk of endometrial cancer. There is evidence of a dose–response relationship; the RR for every 1 cup/day of coffee, caffeinated coffee or decaffeinated coffee is estimated to be 0.95 (95%CI 0.93–0.97), 0.93 (95%CI 0.89–0.97) and 0.96 (95%CI 0.92–0.99), respectively.[118] The protective effect is likely observed only in overweight and obese women and in women who have never used menopausal hormone therapy (MHT).

The evidence is suggestive of an association between intake of green tea and decreased risk of endometrial cancer. A meta–analysis of six studies indicated a dose–response association.[119]

The evidence for an association between black tea and risk of endometrial cancer is inconclusive. There is evidence of no association in meta–analysis of a small number of studies of low quality.

Background

Coffee and caffeine consumption appear to be inversely related to circulating C–peptide levels, especially in overweight and obese women, which can induce tumour development. Further, methylxanthine in coffee may augment the levels of sex–hormone–binding globulin (SHBG) which decrease the concentrations of oestrogen leading to reduced endometrial hyperproliferation. Caffeine has also been shown to be inversely associated with free oestradiol and positively associated with SHBG. Caffeine has been shown to induce glutathione–S–transferases, which in turn deactivate dietary and environmental carcinogens.[118]

Antioxidants in green tea, such as catechins and thearubigins, can induce apoptosis and cell cycle arrest in human carcinoma cells and can inhibit the oestrogen–induced activation of endometrial cells. Catechins, which are at high levels in green tea but are mostly removed from black tea by the fermentation process, have also been shown to act as scavengers of reactive oxygen and nitrogen species and decrease the incidence of cancer.[119]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR 2018)[69] judged the evidence for the association between coffee (independent of caffeine intake) and decreased risk of endometrial cancer to be 'Strong–Probable', based on the systematic review of evidence to 31 December 2012 (CUP Endometrial SLR)[23].

Seven studies contributed to a dose–response meta–analysis for coffee and endometrial cancer. The analysis found that there was a significantly decreased risk of endometrial cancer per one cup of coffee per day (RR 0.93, 95%CI 0.91–0.96). There was evidence of low heterogeneity due to differences in the size of the effect and absence of publication bias.

For decaffeinated coffee, a dose–response meta–analysis of three studies showed a significantly decreased risk of endometrial cancer per one cup per day (RR 0.92, 95%CI 0.87–0.97), with no heterogeneity.

WCRF/AICR (2018)[69] judged the evidence for the association between tea and risk of endometrial cancer to be 'Limited–No conclusion'. In the CUP Endometrial SLR (2012)[23], only two cohort studies contributed to the dose–response meta–analysis, and these studies did not separate exposure to green tea and black tea. There was no association between intake of tea and risk of endometrial cancer (RR per 1 cup/d 1.03, 95%CI 0.89–1.21).

IARC

The International Agency for Research on Cancer (IARC 2018, Volume 116)[120] reviewed more than 1000 studies in humans and animals and found that there was inadequate evidence for the carcinogenicity of coffee drinking overall. It was concluded that 'drinking coffee is not classifiable as to its carcinogenicity to humans (Group 3)'.

The Working Group found evidence suggesting lack of carcinogenicity for cancer of the uterine endometrium, noting the inverse association in many studies.[120] Fourteen cohort and eleven case–control studies were identified investigating the association between coffee intake and risk of cancer of the endometrium. Studies which did not adjust for the important confounders of BMI and smoking were excluded from review. Five meta–analyses published from 2009 to 2015 were also considered. In the summary publication by Loomis et al. (2016)[121] it was indicated that, for endometrial cancer, the five largest cohort studies showed mostly inverse associations with coffee drinking and that these results were supported by the findings of several case–control studies and a meta–analysis.

Recent evidence

Coffee

Five meta–analyses[118, 122-125] and two recent cohort studies[126, 127] were identified for inclusion.

The most recent meta–analysis by Lukic et al. (2018)[122] included 20 studies (12 cohort and 8 case–control studies). Compared with women with lowest coffee intake, women with highest coffee intake were at decreased risk of endometrial cancer (summary RR 0.74, 95%CI: 0.68–0.81). Dose–response analysis showed that 1 additional cup of coffee per day was associated with an RR of 0.97 (95%CI 0.96–0.98) in cohort studies and RR 0.88 (95%CI: 0.82–0.95) in case–control studies. However, in a subgroup analysis based on 5 cohort studies, the association of coffee consumption and decreased risk of endometrial cancer remained significant only in women with a body mass index (BMI) over 30 kg/m^2 (RR 0.71, 95%CI 0.61–0.81).

Zhou et al. (2015)[118] analysed 13 cohort studies, most of which were reviewed by Lukic et al. (2018)[122], and reported a decreased risk of endometrial cancer associated with coffee intake (RR highest vs. lowest intake 0.80, 95%CI 0.74–0.86). Zhou et al. (2015)[118] also found a decreased risk of endometrial cancer associated with highest versus lowest intake of caffeinated coffee (RR 0.66, 95%CI 0.52–0.84), decaffeinated coffee (RR 0.77, 95%CI 0.63–0.94), and caffeine (RR0.77, 95%CI 0.65–0.92). A dose–response analysis revealed a small but significant decreased risk of endometrial cancer. The RR for every 1 cup per day of coffee, caffeinated coffee or decaffeinated coffee was 0.95 (95%CI 0.93–0.97), 0.93 (95%CI 0.89–0.97) and 0.96 (95%CI 0.92–0.99), respectively. The RR per 100 mg caffeine per day was 0.96 (95%CI 0.93–0.98). Subgroup analyses showed that the reduction in risk associated with coffee intake was significant in women with a BMI ≥25 kg/m^2 (RR 0.57, 95%CI 0.46–0.71) and

women who had never used menopause hormone therapy (MHT) (RR 0.60, 95%CI 0.50–0.72) but not in women with a BMI <25 kg/m^2 (RR 0.99, 9% CI 0.86–1.15) and women who had ever used MHT (RR 0.85, 95%CI 0.65–1.11).

The meta–analyses by Lafranconi et al. (2017)[123], which included 9 cohort studies, and Je et al. (2012)[125] which included 6 cohort and 10 case–control studies, both reported a decreased risk of endometrial cancer associated with highest coffee intake versus lowest intake (RR 0.79, 95%CI 0.73–0.87, RR0.71, 95%CI 0.90–0.95, respectively). The decreased risk for 1 cup/day was RR 0.95 (95%CI 0.92–0.97; Lafranconi et al. 2017)[123] and RR 0.92 (95%CI 0.90–0.95; Je et al. 2012)[125]. A meta–analysis by Yang et al. (2015)[124], however, found a weak association for coffee consumption in prospective studies, and suggested that there may have been selective publication of only part of the evidence. The RR per additional cup/day was 0.96 (95%CI 0.95–0.98; 7 prospective studies; high heterogeneity) and 0.91(95%CI 0.87–0.95; 6 retrospective studies; high heterogeneity).

A recent large cohort study of a multiethnic population in Canada (the Canadian Study of Diet, Lifestyle, and Health study) by Park et al (2018)[127] showed no association between coffee drinking and risk of endometrial cancer overall, but coffee drinking was associated with a decreased risk of endometrial cancer among women with a high BMI (≥30 kg/m^2) (HR 0.31, 95%CI 0.14–0.72).[127] Another recent prospective cohort study of 3,185 Canadian women (sample size not large enough to stratify by BMI status) by Arthur et al (2018)[126] showed that each per cup/per day increase in total coffee and caffeinated coffee intake was associated with a 12% decreased risk of endometrial cancer (HR 0.88; 95%CI 0.79–0.95, and 0.88; 0.80–0.96, respectively). The inverse association was not statistically significant for decaffeinated coffee intake and risk of endometrial cancer (HR per cup increase 0.91, 95%CI 0.77–1.08).

Tea

Three meta–analyses[119, 124, 128] and one cohort study[126] were identified for inclusion.

The meta–analysis by Zhou et al. (2016)[119] assessed green tea and black tea separately. Six studies (1 cohort and 5 case–control studies) were included for green tea intake and nine studies (5 cohort and 4 case–control studies) for black tea intake, and risk of endometrial cancer. Compared with the lowest green tea intake, highest green tea intake was associated with a decreased risk of endometrial cancer (RR 0.78, 95 % CI 0.66–0.92; no heterogeneity). A dose–response analysis showed that 1 cup/day of green tea increase was associated with a decreased risk of RR 0.89 (95%CI 0.84–0.94). No association was observed between black tea intake and risk of endometrial cancer (RR 0.99, 95%CI 0.79–1.23). The quality of evidence for the association between green and black tea with risk of endometrial cancer was considered to be moderate and very low, respectively.

Je et al. (2015)[128] found no association between overall tea intake and risk of endometrial cancer in a meta–analysis of five cohort studies (RR for the highest versus lowest category of intake 0.95, 95%CI 0.80–1.12). There was no dose–response association in the meta–analysis of four prospective cohort studies and four retrospective cohort studies by Yang et al. (2015)[124] (RR per cup/day 1.00, 95%CI 0.98–1.02 and 1.04, 95%CI 0.98–1.10; respectively).

The prospective cohort study of 3,185 Canadian women by Arthur et al (2018)[126] showed no association between intake of tea and risk of endometrial cancer (RR per cup/day 1.01, 95%CI 0.90–1.12).

3.5.4 Diet—acrylamide

Evidence summary

Evidence grading: Inconclusive.

The evidence for an association between dietary acrylamide and risk of endometrial cancer is inconclusive. There are a limited number of low quality studies and no evidence of a dose–response. There is some evidence to support a possible association between high dietary acrylamide intake and risk of endometrial cancer among women who have never smoked.

Background

Acrylamide is a water soluble white solid used in industries such as papermaking, building constructions and water treatment. Dietary acrylamide is formed during high–temperature cooking as a result of degradation of lipid, carbohydrates, or free amino acids, dehydration/decarboxylation of organic acids, and direct formation from amino acids. It is found in foods such as potato crisps, fried potatoes, french fries, cookies and coffee.

Several mechanisms have been proposed to associate acrylamide and endometrial cancer. Acrylamide is metabolised by CYP2E1 enzyme to glycidamide, a chemically reactive epoxide which has been shown to be mutagenic in animals, and there is some evidence of carcinogenicity of acrylamide in experimental animal studies. Also, it is hypothesised that dietary acrylamide may affect the activity of enzymes involved in the metabolism of sex steroid hormones leading to prolonged exposure to increased oestrogen levels.[129]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR 2018)[69] judged the evidence for the association between dietary acrylamide and risk of endometrial cancer to be 'Limited–No conclusion', based on the systematic review of evidence to 31 December 2012 (CUP Endometrial SLR)[23].

Three cohort studies contributed to the dose–response meta–analysis for dietary acrylamide and risk of endometrial cancer. The summary RR per 10 µg/day dietary acrylamide intake was 1.07 (95%CI 0.94–1.21).

Recent evidence

Two meta–analyses were identified for inclusion.[129, 130]

Je et al. (2015)[129] included four prospective cohort studies and reported that, compared to women with low dietary acrylamide intake, there was no significantly increased risk of endometrial cancer for women with high intake (RR 1.10, 95%CI 0.91–1.34). A dose–response analysis did not show an association between 10 µg/d dietary acrylamide intake and risk of endometrial cancer (RR 1.04, 95%CI 0.97–1.11). High dietary acrylamide intake was significantly associated with increased risk of endometrial cancer in women who never smoked (RR for high vs.low intake 1.39, 95%CI 1.09–1.77). The risk of bias was rated overall to be high.

Similar findings were reported by Pelucchi et al. (2015)[130] who conducted a meta–analysis of the same four cohort studies identified by Je et al. (2015)[129, 130]. No association was observed between high dietary acrylamide intake and risk of endometrial cancer in women who were ever smokers (RR for high vs. low intake 1.06, 95%CI 0.92–1.23). A borderline significant association for high versus low dietary acrylamide intake and risk of endometrial cancer was seen among never–smokers (RR 1.23, 95%CI 1.00–1.51). The authors concluded that a modest association for high intake of dietary acrylamide and increased risk of endometrial cancer in never smokers cannot be excluded.

3.5.5 Diet—fat

Evidence summary

Evidence classification: Inconclusive.

The evidence for an association between dietary fat or cholesterol consumption and risk of endometrial cancer is inconclusive. Findings across studies are inconsistent and the studies are limited in quality due to high risk of bias. Most meta–analyses have reported no association between intake of various types of dietary fat and risk of endometrial cancer.

Background

Studies have shown that higher fat intake is associated with increased circulating oestradiol, insulin secretion, insulin–like growth factors (IGFs) levels, and inflammatory molecules including C–reactive protein, intracellular adhesion molecule–1 and interleukin–6. Excessive fat consumption could therefore promote endometrial cancer development through unbalanced hormone, insulin, and IGFs levels, as well as inflammatory responses.[131]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR 2018)[69] judged the evidence for an association between dietary fat including 'total fat', 'animal fat', 'cholesterol' and 'saturated fatty acids' and endometrial cancer as 'Limited–no conclusion'.

The WCRF/AICR systematic review of evidence to December 2012 (CUP Endometrial SLR)[23] only provided an evidence update for 'total fat'. A meta–analysis of three cohort studies showed no association between dietary fat intake and risk of endometrial cancer (RR per 10 g fat per day 1.00, 95%CI 0.96–1.04; high heterogeneity due to limited number of studies). The CUP Endometrial SLR (2012)[23] reported on the findings of a meta–analysis of seven case–control studies by Bandera et al. (2007)[132] which found, after excluding studies that did not adjust for total energy intake, a suggested increased risk (RR 1.17, 95%CI 1.08–1.28; no heterogeneity).

Recent evidence

Four meta–analyses were identified for inclusion.[131, 133-135]

Zhao et al. (2016)[131] included 21 studies (7 cohort and 14 case–control studies) and included multiple analyses pooled by study type. The results of the analyses were inconsistent between cohort and case–control study types, with no consistent association between any of the dietary fat measures and risk of endometrial cancer. Based on pooled results from cohort studies, total fat, saturated fat, polyunsaturated fatty acids or linoleic acid intake was not associated with risk of endometrial cancer (RR for highest category vs. lowest category of intake = 0.91, 95%CI 0.83–1.01; 0.91, 95%CI 0.80–1.03; 0.94, 95%CI 0.78–1.12; and, 1.08, 95%CI 0.95–1.23, respectively).

The meta–analysis by Gong et al. (2016)[133] included sixstudies (1 cohort and 5 case–control studies). The pooled dose–response analysis of cholesterol consumption found a 6% increased risk of endometrial cancer per 100 mg/d of cholesterol consumed (OR 1.06, 95%CI 1.00–1.12). The result had borderline statistical significance and the analysis was affected by significant heterogeneity (I^2 = 64.2%, P for heterogeneity = 0.003).

Neither of the meta–analyses by Jiang et al. (2015)[134] and Wu et al. (2015)[135] found an association between any of the dietary fat measures and risk of endometrial cancer. Jiang et al. (2015)[134] included nine cohort studies and reported an RR per 30g per day total fat intake of 0.98 (95%CI 0.95–1.00). Wu et al. (2015)[135] included three cohort and 10 case–control studies and reported a RR per 10g per day saturated fatty acids intake of 1.02 (95%CI 0.97–1.08). In the latter meta–analysis, 10 g per day intake of monounsaturated fatty acids or polyunsaturated fatty acids was not associated with risk of endometrial cancer (RR 0.98, 95%CI 0.96–1.00 and RR 1.00, 95%CI 0.95–1.06, respectively.)

3.5.6 Diet—glycaemic load

Evidence summary

Evidence grading: Probable.

Glycaemic load (GL) is probably associated with an increased risk of endometrial cancer. A number of meta–analyses have shown an increased risk of endometrial cancer associated with a higher GL intake versus lower GL intake and there is evidence of a dose–response relationship. However, several large cohort studies have not found any association. The increased risk of endometrial cancer associated with GL has been estimated as1.15 (95%CI 1.06–1.25) per 50 units GL per day.[69]

Background

The glycaemic load (GL) of food is a number that estimates how much the food will raise a person's blood glucose level after consumption. One unit of GL is approximately equivalent to the effect of consuming one gram of glucose. Glycaemic load is based on the glycaemic index (GI) and is calculated by multiplying the grams of available carbohydrate in the food with the food's GI and then dividing by 100.

Several mechanisms have been proposed for the association of GL with risk of endometrial cancer. Long–term consumption of a high glycaemic diet results in hyperinsulinemia. Hyperinsulinemia increases the bioavailability of insulin–like growth factor 1 (IGF–1) which can promote the development of endometrial cancer by enhancing cellular proliferation and

reducing apoptosis. Insulin and IGF–1 are also powerful negative regulators of sex hormone–binding globulin (SHBG) synthesis in vitro and thus may stimulate endometrial cancer risk through a hormonal pathway. High GL may also increase risk of endometrial cancer by enhancing oxidative stress.[136]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR 2018)[69] judged the evidence for the association between glycaemic load and increased risk of endometrial cancer to be 'Strong–probable', based on the systematic review of evidence to 31 December 2012 (CUP Endometrial SLR)[23]. The WCRF/AICR (2018)[69] concluded that 'there is a substantial amount of generally consistent evidence from cohort studies, and there is evidence of biological plausibility'.

Six cohort studies were included in the dose–response meta–analysis for GL and risk of endometrial cancer. There was a statistically significant increased risk of endometrial cancer per 50 units per day (RR 1.15, 95%CI 1.06–1.25), with no evidence of heterogeneity.

Recent evidence

Three meta–analyses were identified for inclusion.[136-138]

Nagle et al. (2013)[136] included two case–control studies not included in the analysis by WCRF/AICR (2018)[69]. Several factors were adjusted for including BMI and energy intake (in all studies) and, variously, smoking, physical activity, age at menopause/menarche, and use of oral contraceptive pill and menopausal hormone therapy. The RR for endometrial cancer in the highest versus lowest category of GL intake was 1.21(95%CI 1.09–1.33). A dose–response analysis revealed a 6% increase in risk of endometrial cancer per 50–unit increase in GL intake (RR 1.06, 95%CI 1.01–1.11).

A more recent meta–analysis by Turati et al. (2015)[137] included three additional observational studies (two case–control and one cohort study) in addition to the eight studies included by Nagle et al (2013)[136]. Analysis of the highest category[ix] versus lowest category of GL intake and risk of endometrial cancer showed a RR of 1.17 (95%CI 1.00–1.37), with high heterogeneity likely associated with inclusion of the cohort study by Coleman et al (2014)[139]. This latter study was the only included study to show a decreased risk of endometrial cancer associated with higher GL intake (RR 0.63, 95%CI 0.47–0.85).

A meta–analysis by Galeone et al. (2013)[138] included a sub–set of seven studies that were included by Turati et al. (2015)[137] and indicated an increased risk of endometrial cancer of 1.19 (95%CI 1.06–1.34) associated with the highest versus lowest category of GL intake.

Sieri et al. (2017)[140], in an analysis of data from the prospective EPIC–Italy study, found that the risk of endometrial cancer increased with increasing GL quintiles, however the increases were not significant (P trend was 0.176). These authors noted, however, that there were only

[ix] Across the studies, the 'highest' category is defined as follows: median 118 and ranges greater than 136 to 200. Across the studies the 'lowest' category is defined as follows: median 73 and ranges below 67 to 164.

203 cases in their analysis, hence insufficient power may have been the cause of the insignificant association.

Hartman et al (2018)[141] conducted an analysis of data from the Cancer Prevention Study II (CPS–II) Nutrition Cohort, with a median follow–up of 13.6 years and 425 cases of endometrial cancer among postmenopausal women. There was no association between GL intake and risk of endometrial cancer (RR 1.00, 95%CI 0.77–1.31; RR 1.01, 95%CI 0.77–1.33); RR 0.83, 95%CI 0.62–1.11; p trend = 0.25; for GL intake of <100.47, 100.47–<113.70, 113.70–<126.82, ≥126.82, respectively).

3.5.7 Environmental tobacco smoke

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between exposure to environmental tobacco smoke (passive smoking; second–hand smoke) and risk of endometrial cancer is inconclusive. Very limited studies in quantity and quality are available.

Background

Environmental tobacco smoke (ETS) is the combination of the smoke that a smoker breathes out and the smoke that comes directly from their burning cigarette or other tobacco product. This smoke contains the same carcinogens that are inhaled by smokers, although the concentrations of individual components vary according to how easily the smoke can be dispersed into the environment.[142]

IARC

The International Agency for Research on Cancer (IARC 2012, Volume 100E)[103] concluded that there is sufficient evidence in humans for the carcinogenicity of second–hand tobacco smoke and that second–hand tobacco smoke is carcinogenic to humans (Group 1). Second–hand tobacco smoke causes cancer of the lung and a positive association has been observed between exposure to second–hand tobacco smoke and cancer of the larynx and pharynx. No evidence in humans was included for endometrial cancer.

Recent evidence

One meta-analysis was identified.[143]

The meta–analysis by Lee et al. (2016)[143] included five studies (3 cohort and 2 case–control studies) from Japan, Poland and Europe. Exposure versus no exposure to environmental tobacco smoke from a spouse or cohabitant among non–smoking women was not associated with risk of endometrial cancer (RR 0.88, 95%CI 0.78–1.01). Individual studies were of mixed quality and the meta–analysis was funded by the Japanese tobacco industry, therefore risk of bias is likely to be high.

3.5.8 Physical activity

Evidence summary

Evidence classification: Probable.

Physical activity is probably associated with a decreased risk of endometrial cancer. There is evidence that body mass index (BMI) may mediate the association between physical activity and endometrial cancer risk as the association is mainly observed among overweight and obese women (BMI ≥25 kg/m^2). The decreased risk of endometrial cancer associated with the highest versus lowest levels of [any] physical activity has been estimated as 0.80 (95%CI 0.75–0.85).[144] Risk estimates are similar across different types of physical activity (recreational, occupational, household, walking or biking).

It is estimated that 6% of endometrial cancers are attributable to insufficient (less than 30 MET–hours[x] per week) physical activity.[145]

Background

Physical activity is defined as any bodily movement produced by skeletal muscle that requires energy expenditure. Evaluating the association between physical activity and cancer is hampered by differences in exposure definition across studies. Physical activity can be categorised into occupational, recreational or other types of activity, and measured in terms of frequency, duration and intensity. Different types of activity are commonly equated through metabolic equivalents (MET). The World Health Organization defines moderate–intensity physical activity as any activity with an MET value between 3 and 5.9 and vigorous–intensity physical activity as ≥6 MET (WHO 2010). Physically inactive people are those who are performing insufficient amounts of moderate– and vigorous–intensity activity.[146]

Recommended levels of physical activity in Australia are at least 150 minutes of moderate intensity physical activity or 75 minutes of vigorous physical activity per week to help improve blood pressure, cholesterol, heart health and muscle and bone strength. This should be increased to 300 minutes of moderate intensity physical activity or 150 minutes of vigorous intensity physical activity per week to reap greater health benefits and help to prevent cancer and unhealthy weight gain.[110, 147]

Physical activity is hypothesised to decrease risk of endometrial cancer because it reduces oestradiol levels and increases the sex hormone binding globulin (SHBG) which is the binding protein for oestradiol. Effects on oestrogen metabolism may at least in part operate directly, or through decreasing body fat stores.[69]

Hyperinsulinaemia also promotes endometrial carcinogenesis by stimulating endometrial cell growth directly or indirectly through increasing insulin–like growth factor (IGF)–1 levels within the endometrium and decreasing levels of its binding proteins. The effects of physical activity in reducing insulin levels and insulin resistance also contribute to decreased endometrial cancer risk.[69]

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[x] One MET (metabolic equivalent) is defined as energy expenditure at rest, equivalent to 3.5 ml of oxygen uptake per kilogram per minute. 30 MET–hours per week is equivalent to 300 minutes of moderate–intensity physical activity.

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR 2018)[69] judged the evidence for the association between physical activity (all types – occupational, household, transport and recreational) and decreased risk of endometrial cancer to be 'Strong–probable', based on the systematic review of evidence to 31 December 2012 (CUP Endometrial SLR)[23]. The WCRF/AICR (2018)[69] noted that '*there is generally consistent evidence showing lower risk of cancer of the endometrium with higher levels of physical activity and there is strong evidence of mechanisms operating in humans*'.

A dose response analysis was not possible due to the differences in the assessment of physical activity across studies. Eight of nine studies showed a decreased risk of endometrial cancer when comparing the highest versus lowest levels of recreational physical activity; after adjusting for BMI, the decreased risk was 0.73 (95%CI 0.58–0.93; 9 studies). The decreased risk of endometrial cancer for highest versus lowest levels of occupational physical activity was 0.79 (95%CI 0.71–0.88; 5 studies). Three of the five studies assessing physical activity from walking or biking (mainly for transportation) reported a decreased risk of endometrial cancer, one of which was significant, when comparing highest versus lowest levels (RR 0.89, 95%CI 0.69–1.14; 5 studies).

Recent evidence

Four studies were identified for inclusion: one pooled analysis[148], two meta–analyses[144, 149] and one cohort study[150].

The individual patient data (IPD) analysis by Moore et al. (2016)[148] excluded women without an intact uterus from the control group and provided sensitivity analyses based on BMI and smoking. Nine prospective cohort studies participating in the Physical Activity Collaboration of the National Cancer Institute's Cohort Consortium (PAC/NCICC) were included in the analysis. Women with a higher level of leisure–time physical activity (90th percentile) compared with a lower level of leisure–time physical activity (10th percentile) had a decreased risk of endometrial cancer (HR 0.79, 95%CI 0.68–0.92). Stratification by BMI, however, showed that BMI is a significant effect modifier (P<0.001), with no association between higher (90th percentile) compared to lower (10th percentile) levels of leisure–time physical activity and endometrial cancer risk in those who are not overweight (BMI <25 kg/m^2; HR 0.98, 95%CI 0.89–1.09[3]); and a significantly decreased risk of endometrial cancer for higher versus lower levels of leisure–time physical activity among those who are overweight or obese (BMI ≥25 kg/m^2; HR 0.83, 95%CI 0.69–0.94[xi]).

The meta–analysis by Schimd et al. (2015)[144] included 33 studies (19 cohort and 14 case–control studies). A significant association was reported for any form of physical activity and decreased risk of endometrial cancer for high compared with low[xii] levels (RR 0.80, 95%CI 0.75–0.85). However, as per the pooled analysis, when stratified by BMI, no significant association was seen for women with a BMI of less than 25 kg/m^2 (RR 0.97, 95%CI 0. 84–1.13; 7 studies) but the association was significant among overweight or obese women (BMI ≥25kg/m^2; RR 0.69, 95%CI 0.52–0.91; 7 studies). Higher versus lower levels of specific forms of

[xi] Estimated values from Figure 2, Moore et al (2016)
[xii] Various definitions of 'high' and 'low' levels of physical activity across studies

physical activity, including recreational, occupational and walking, were all associated with decreased risk of endometrial cancer (RR 0.84, 95%CI 0.78–0.91 (22 studies), RR 0.81, 95%CI 0.75–0.87 (19 studies) and RR 0.82, 95%CI 0.69–0.97 (10 studies), respectively). Higher versus lower levels of household physical activity was associated with a non–significant decreased risk (RR 0.70, 95%CI 0.47–1.02; 7 studies).

Keum et al. (2014)[149] conducted a dose–response meta–analysis by MET–hour/week and reported a summary RR for each 3 MET–hour/week increase in leisure–time physical activity of 0.98 (95%CI 0.95–1.00; 3 cohort studies and 3 case–control studies) and an increase by an hour/week was associated with a reduced risk of 0.95 (95%CI 0.93–0.98; 2 cohort studies and 4 case–control studies). The authors concluded that the dose–response relationship was evident within the physical activity ranges of 0–50 MET–hours/week or 0–15 hours/week.

The Norwegian Women and Cancer (NOWAC) cohort study as reported by Borch et al. (2017)[150] involved 82,759 women aged 30–70 years with different BMI profiles. Overall, the risk of endometrial cancer decreased with increasing levels of physical activity (all types) in a dose–response manner, independent of BMI. A significant association between low physical activity levels at baseline and follow-up and endometrial cancer risk was found (lowest level: HR 1.60, 95%CI 1.16–2.20; highest level: HR 0.73, 95%CI 0.45–1.16 compared to the median). When analyses were stratified by BMI category, physical activity was not associated with overall endometrial cancer among normal-weight women in analyses using baseline data only (HR physical activity scores 1–2 vs. 5–6: 1.32, 95%CI 0.71–2.45), despite the interaction between physical activity and BMI being not significant (p = 0.49). The corresponding association in obese women was 3.08 (95%CI 1.76–5.39). The authors concluded that while physical activity lowered risk of endometrial cancer overall, the potential for residual confounding by BMI remains.

3.5.9 Sedentary behaviour

Evidence summary

Evidence classification: Suggestive.

The evidence is suggestive of an association between various measures of sedentary behaviour and an increased risk of endometrial cancer. Although the majority of studies indicate a positive association and there is evidence of a dose–response relationship, the evidence is limited by the possibility of confounding, particularly by body mass index (BMI).

Background

Sedentary behaviour is not the same as physical inactivity and is defined as any waking behaviour characterised by an energy expenditure ≤1.5 METs[xiii] while in a sitting, reclining or

[xiii] One MET (metabolic equivalent) is defined as energy expenditure at rest, equivalent to 3.5 ml of oxygen uptake per kilogram per minute (Wilson et al. 2019). The World Health Organization defines moderate–intensity physical activity as any activity with an MET value between 3 and 5.9 and vigorous–intensity physical activity as ≥6 MET (WHO 2010).

lying posture. Physical inactivity refers to performing insufficient amounts of moderate– and vigorous–intensity activity.[146]

Spending excessive amounts of time sitting is associated with increased risk of insulin resistance, which increases the risk of endometrial cancer. Sitting time may also be linked to endometrial cancer risk through insulin–related mechanisms via low levels of energy expenditure, as well as via weight gain, which are both associated with sitting time.[69]

WCRF/AICR

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR 2018)[69] judged the evidence for the association between sedentary habits (as marked by sitting time) and increased risk of endometrial cancer to be 'Limited–suggestive', based on the systematic review of evidence to December 2012 (CUP Endometrial SLR)[23].

A dose response analysis was not possible, but three cohort studies indicated a positive association between sedentary behaviour as measured by highest versus lowest sitting time and increased risk of endometrial cancer. After adjusting for Body Mass Index (BMI), however, only one study reported a significant association and confounding could not be excluded. The RR for endometrial cancer in women with highest versus lowest time spent sitting was estimated as RR 1.46 (95%CI 1.21–1.76).

Recent evidence

Two meta–analyses were identified for inclusion.[151, 152]

The meta–analysis by Schmid et al. (2014)[151] included eight studies (2 cohort and 6 case–control studies) and reported a significant association between time spent sedentary and risk of endometrial cancer. Several factors were adjusted for including age (all studies), physical activity (2 studies) and Body Mass Index (BMI; 2 studies). The RR for endometrial cancer in women with highest versus lowest time spent sedentary groups was 1.36 (95%CI 1.15–1.60; 8 studies). A dose–response analysis indicated a 10% increase in risk of endometrial per 2 hours spent sedentary per day (RR 1.10, 95%CI 1.05–1.15; 8 studies). Results were consistent when analyses were conducted including studies that did or did not adjust for different potential confounders including physical activity, adiposity, smoking, dietary factors, alcohol consumption, and study quality. The only exceptions were when the analysis was limited to a single study that adjusted for alcohol (no significant association), and three studies with a low–quality rating (no significant association). Significant positive associations were also identified for total sitting time (RR highest vs. lowest 1.32, 95%CI 1.08–1.61; 2 studies) and TV viewing time (RR highest vs. lowest 1.66, 95%CI 1.21–2.28; 1 study) but not occupational sitting time (RR highest vs. lowest 1.11, 95%CI 0.88–1.39; 4 studies).

The meta–analysis by Shen et al. (2014)[152] included three cohort studies, two of which were included in the meta–analysis by Schmid et al. (2014)[151] and in the meta–analysis by WCRF/AICR (2012)[23]. The increased risk of endometrial cancer in women with highest compared to lowest time spent sedentary was RR 1.28 (95%CI 1.08–1.53).

3.5.10 Tobacco smoking

Evidence summary

Evidence classification: Convincing (postmenopausal).

There is convincing evidence that tobacco smoking is associated with a decreased risk of endometrial cancer. This association has been observed particularly among postmenopausal women. Pooled analyses of large numbers of cohort and case–control studies indicate an inverse association between current or former smoking and risk of endometrial cancer risk. There is evidence of a dose–response relationship. The decreased risk of endometrial cancer (Type 1) associated with current and former smoking has been estimated as 0.64 (95%CI 0.60–0.70) and 0.87 (95%CI 0.82–0.91), respectively.[14]

Background

Tobacco smoking is the practice of burning tobacco and inhaling the smoke (consisting of particle and gaseous elements). Tobacco smoke is a complex mixture of over 5,300 compounds, including toxicants and known carcinogens.[142]

Smoking may lower endometrial cancer risk through anti–oestrogenic mechanisms. Smoking can alter oestrogen metabolism and favour production of 2–hydroxyestrone which leads to anti–carcinogenic effects, an increase in progesterone levels and a lower age at menopause due to destruction of oocytes. In addition, cigarette smokers tend to be leaner than non–smokers, which would result in a reduced conversion of androstenedione to oestrogen in adipose tissue.[14, 153]

IARC

The International Agency for Research on Cancer (IARC 2012, Volume 100E)[103] concluded that tobacco smoking is carcinogenic to humans (Group 1) and there is sufficient evidence in humans for the carcinogenicity of smoking. Tobacco smoking causes cancers of the lung, oral cavity, naso–, oro– and hypopharynx, nasal cavity and accessory sinuses, larynx, oesophagus, stomach, pancreas, colorectum, liver, kidney (body and pelvis), ureter, urinary bladder, uterine cervix and ovary, and myeloid leukemia. Also, a positive association has been observed between tobacco smoking and female breast cancer.

For endometrial cancer specifically, IARC examined 42 studies and concluded that there is evidence suggesting lack of carcinogenicity of tobacco smoking for cancer of the endometrium (postmenopausal).[103] The Working Group noted that 'The results of epidemiological studies to date, including recent studies, largely show inverse associations of smoking with risk of postmenopausal endometrial cancer'. However, the few studies of premenopausal cancer were less consistent with some studies showing a decreased risk, some studies showing no association and several studies, including a multicentre European study, showing an increased risk among smokers.

Recent evidence

Two pooled analyses were identified for inclusion.[14, 62] Both analyses were based on cohort and case–control studies participating in the Epidemiology of Endometrial Cancer Consortium (E2C2[xiv]). An additional prospective cohort study[153] not included in either of the pooled analyses and a recent retrospective cohort study[154] were also sourced.

The individual patient data (IPD) analysis by Setiawan et al. (2013)[14] excluded women without an intact uterus from the control group and provided sensitivity analysis based on study type and source of histological classification. Twenty–three studies (10 cohort and 13 case–control studies) were included in the pooled analysis for smoking, and current smoking versus never smoking was associated with a decreased risk of type I and type II endometrial cancer (OR 0.64, 95%CI 0.60–0.70 and OR 0.60, 95%CI 0.46–0.77, respectively). Former smoking versus never smoking was also associated with a decreased risk of type I and type II endometrial cancer (OR 0.87, 95%CI 0.82–0.91 and OR 0.70, 95%CI 0.59–0.83, respectively). Based on 18 studies with pack–years of smoking data, similarly decreased risks of endometrial cancer were observed when comparing <20 pack–years with never smoking and ≥20 pack–years with never smoking, with evidence of an inverse dose–response association (OR 0.86, 95%CI 0.80–0.92 and OR 0.71, 95%CI 0.65–0.77, respectively for type I endometrial cancer). Analysis restricted to postmenopausal women who never used menopausal hormones yielded similar results.

Very similar findings were reported by Cote et al. (2015)[62] in a pooled analysis of data (15099 controls; 6209 cases) from 7 cohort and 4 case–control studies (five (4 cohort, 1 case–control) of which were not included by Setiawan et al. 2013), to identify and compare risk factors for endometrial cancer in black women and in white women in the US. Cigarette smoking was reported to be associated with a decreased risk of endometrial cancer among all women. Current versus never smoking was associated with a decreased risk of endometrial cancer among black women and among white women (OR 0.67, 95%CI 0.47–0.95 and OR 0.63, 95%CI 0.56–0.72, respectively). Former versus never smoking was also associated with a decreased risk of endometrial cancer among black women and among white women (OR 0.72, 95%CI 0.56–93 and OR 0.85, 95%CI 0.79–0.91, respectively).

An earlier meta–analysis by Zhou et al. (2008)[155] stratified findings by study type and menopausal status. Meta–analysis of 14 case–control studies showed a decreased risk of endometrial cancer associated with smoking among postmenopausal women (OR 0.71, 95%CI 0.65–0.78) but no association between smoking and risk of endometrial cancer among premenopausal women (OR 1.06, 95%CI 0.88–1.28; 8 case–control studies).

Felix et al. (2014)[153] reported on findings from the prospective National Institutes of Health–AARP Diet and Health Study in the US. Among110 304 women, 1,476 incident cases of endometrial cancer were identified. Former smoking and current smoking was associated (RR 0.89, 95%CI 0.80–1.00 and RR 0.65, 95%CI 0.55–0.78; respectively) with a decreased risk of endometrial cancer compared with never smoking. Smoking cessation 1–4 years prior to baseline was significantly associated with decreased risk of endometrial cancer (RR 0.65, 95%CI 0.48–0.89), while cessation ≥10 years before baseline was not. The association was not

[xiv] E2C2 is an international consortium formed in 2006 to provide a collaborative environment to address questions around endometrial cancer by pooling data from existing studies that would be underpowered in individual studies. To date, it includes data from more than 40 studies from the United States, Canada, Europe, Asia and Australia.

modified to a statistically significant level by any endometrial cancer risk factor, including BMI. Menopausal status was the only factor suggestive of modifying the relationship, with lower risk of endometrial cancer among postmenopausal but not premenopausal women.

Jacob et al. (2018)[154] analysed data on the impact of smoking on 25 different cancers in 422 010 patients visiting General Practitioners in the UK, followed for up to 30 years. In this retrospective cohort study, incidence of endometrial cancer was significantly lower in female smokers compared with non–smokers (HR 0.60, 95%CI 0.48–0.76 among all women and HR 0.54, 95%CI 0.37–0.79 among women aged 50–70 years at index date).

3.5.11 Weight loss

Evidence summary

Evidence classification: Suggestive.

The evidence is suggestive of an association between intentional weight loss (surgical and non–surgical) and decreased risk of endometrial cancer among obese women. Studies are limited in number and quality, but findings are generally consistent.

It is estimated that 24.2–36.0% of endometrial cancer cases could be avoided during 2013–2037 if overweight and obesity were eliminated in the Australian population.[110]

Background

Weight gain and being overweight or obese is significantly associated with an increased risk of endometrial cancer. Body fatness is known to increase the risk of endometrial cancer through a number of mechanisms including elevated circulating oestrogen levels which can promote cancer development. Therefore, it would be expected that weight loss in women who are overweight or obese would be likely to reduce this risk.[6]

Recent evidence

The prospective cohort study by Luo et al. (2017)[6] included 36,794 women aged 50 to 79 years participating in the 'Women's Health Initiative' in the US, followed for an average of 10 years. After analyses were adjusted for baseline body mass index (BMI) and other potential confounders, postmenopausal women who had intentional weight loss ≥5% over the first 3 years of follow–up had a significantly decreased risk of endometrial cancer compared to women who had maintained a stable weight (HR 0.71; 95%CI 0.54–0.95). The risk was lower for obese women at baseline who had intentional weight loss over the first three years of follow–up (HR 0.44; 95%CI 0.25–0.78). Stratified analyses for healthy weight, overweight and obese women found significant associations with endometrial cancer risk only for obese women. Overweight or obese women who achieved a healthy weight after choosing to lose weight had the same risk as women who maintained a healthy weight. Subgroup analyses suggested that the association may be restricted to intentional weight loss (≥5% of starting weight), while equivalent unintentional weight loss was not associated with a significant risk reduction.

In a study of two cohorts of Japanese women (n=40,422), Wakamatsu et al. (2019)[156] reported that, compared to those with a stable weight since aged 20, weight loss since age 20 tended to be associated with a decreased risk of endometrial cancer (HR 0.46, 95%CI 0.21–1.00; 88 cases).

Other studies have focused on risk of endometrial cancer associated with weight loss following bariatric surgery.

Two recent retrospective, population–based cohort studies used data from the Hospital Episodes Statistics database in England, collected during similar time periods, to examine any association between bariatric surgery and risk of endometrial cancer among obese women.[157, 158] MacKenzie et al. (2018)[157] analysed data from a cohort of 716,960 patients diagnosed with obesity, of whom 8,794 patients underwent bariatric surgery. These patients were matched with the same number of patients who did not have surgery. Obese women who had bariatric surgery had a significantly decreased risk of endometrial cancer compared to obese women who did not have bariatric surgery (OR 0.21; 95%CI 0.13–0.35).[157] Bariatric surgery using gastric bypass was associated with the largest risk reduction (OR 0.08; 95%CI 0.03–0.22) (however this procedure was also associated with a two–fold increased risk of colorectal cancer (OR 2.63; 95%CI 1.17–5.95)). Aravani et al. (2018)[158] examined incidence of endometrial cancer in obese women who did and did not have bariatric surgery compared to the background population. Risk of endometrial cancer in a median follow–up period of 3 years, was increased to a similar degree for both groups (Standardised Incidence Ratio (SIR) 2.98, 95%CI 2.25–3.90, for surgery (n=54 cases) and SIR 2.60, 95%CI 2.48–2.73, for non–surgery (n=1758 cases)) compared with the background population. Considerable limitations to the data were noted.

Schauer et al. (2019)[159] conducted a retrospective cohort study of patients undergoing bariatric surgery (22,198 subjects matched to 66,427 nonsurgical subjects). After a mean follow–up of 3.5 years, the risk of endometrial cancer was significantly decreased among those who had undergone bariatric surgery compared with matched nonsurgical patients (HR 0.50; 95%CI 0.37–0.67).

A meta–analysis of studiespublished between 2008 and 2014 by Winder et al. (2018)[160] investigated the incidence of endometrial cancer after bariatric surgery. Bariatric surgery was associated with a decreased risk of endometrial cancer (OR 0.317; 95%CI 0.161–0.627), although there was high heterogeneity between studies. The high heterogeneity between studies was also noted in a review by Aubrey et al. (2019)[161], and was deemed too high to allow quantitative analysis.

3.6 Medical factors

3.6.1 Non–steroidal anti–inflammatory drugs (NSAIDs)

Evidence summary

Evidence classification: Suggestive (in obese women).

The evidence is suggestive of an association between the regular use of non–steroidal anti–inflammatory drugs (NSAIDs–aspirin or non–aspirin) and decreased risk of endometrial cancer, but only among obese women (Body Mass Index (BMI) ≥30.0 kg/m^2) and possibly also among overweight women (BMI 25.0–29.9 kg/m^2). A pooled analysis and several meta–analyses indicate no association between ever or regular use of aspirin or other NSAIDs and risk of endometrial cancer among women of healthy weight.

Background

NSAIDs are anti–inflammatory medications that inhibit COX–1 and COX–2 enzymes reducing prostaglandin synthesis. Aspirin is a non–selective NSAID that is commonly used for relieving pain, fever and inflammation, and in low doses used as an antiplatelet drug to reduce risk of cardiovascular events. A protective effect against colorectal cancer, has been established by observational studies. Anti–inflammatory medications might be more protective among obese women because obesity is associated with chronic low–grade inflammation. In addition, the ability of NSAIDs to down–regulate aromatase activity which is essential for oestrogen formation in fatty tissues in postmenopausal women, may mitigate some of the excess endometrial cancer risk associated with obesity.[162]

Recent evidence

Five studies were identified for inclusion, one was a pooled analysis[162] and four were meta–analyses.[163-166]

Webb et al. (2019)[162] conducted a pooled analysis of 7 cohort and 5 case–control studies participating in the Epidemiology of Endometrial Cancer Consortium, including 7,120 women with endometrial cancer and 16,069 controls. At least weekly use of aspirin or other NSAIDs compared to never use was associated with a decreased risk of endometrial cancer among overweight and obese women (OR 0.86, 95%CI 0.76–0.98 and OR 0.86, 95%CI 0.76–0.97, respectively for aspirin; OR 0.87, 95%CI 0.76–1.00 and OR 0.84, 95%CI 0.74–0.96, respectively for other NSAIDs). No association between use of aspirin or other NSAIDs and endometrial cancer risk was found among women of normal weight (BMI <25 kg/m^2) (OR 1.05, 95%CI 0.93–1.18 for aspirin and OR 1.11, 95%CI 0.97–1.27 for other NSAIDs). The reduced risk of endometrial cancer was only observed among overweight and obese women who used aspirin 2–6 times per week (OR 0.81, 95%CI 0.68–0.96), but not among those who used it daily (OR 0.91, 95%CI 0.80–1.03), possibly due to use of low–dose formulations (to prevent heart disease) by the daily users.

Verdoodt et al. (2016)[164] conducted a meta–analysis, rather than a pooled analysis, of the same studies as Webb et al. (2019)[162]. No overall statistically significant associations were

identified between regular use versus no use of aspirin or other NSAIDs and risk of endometrial cancer. The RR for regular use of non–aspirin NSAIDs compared to non–use was 0.94 (95%CI 0.83–1.05) for cohort studies and 0.91 (95%CI 0.81–1.03) for case–control studies. The RR for regular use of aspirin compared to non–use was 0.92 (95%CI 0.84–1.00) for cohort studies and 0.89 (95%CI 0.79–1.01) for case–control studies. A decreased risk of endometrial cancer was observed, however, with regular aspirin use versus non–use among obese women, but only in case–control studies and not cohort studies (OR 0.56, 95%CI 0.33–0.95 and OR 0.80, 95%CI 0.56–1.14, for case–control and cohort studies respectively).

Three meta–analyses examined use of aspirin only, not other NSAIDs.[163, 165, 166] The meta–analysis by Qiao et al. (2018)[163] included 14 studies (8 cohort and 6 case–control studies), six of which were included by Webb et al. (2019)[162]. The use of aspirin was associated with a decreased risk of endometrial cancer (RR 0.92; 95%CI 0.85–0.99); however subgroup analyses revealed no statistically significant associations when risk was stratified by study design, exposure assessment, and duration of use (less than or more than 5 years of use). The meta–analysis by Zhang et al. (2016)[165] included the same studies as Verdoot et al. (2016)[164] and ever use versus no use of aspirin was associated with a decreased risk of endometrial cancer (RR 0.93, 95%CI 0.88–0.99; no substantial statistical heterogeneity). A doseresponse analysis showed a 3% decreased risk of endometrial cancer per additional dose of aspirin per week (RR 0.97, 95%CI 0.95–0.99). In subgroup analyses, higher dosage or higher frequency of aspirin use was significantly associated with a reduced risk of endometrial cancer. However long–term aspirin use was found to be associated with decreased endometrial cancer risk only among obese women.

Neill et al. (2013)[166] similarly identified increased risk only among obese women. In a meta–analysis of a sub–set of studies (4 cohort and 4 case–control) included in the more recently published meta–analyses, the overall pooled risk estimate for 'any aspirin use' versus 'no use of aspirin' was 0.87 (95%CI 0.79–0.96; no evidence of heterogeneity). When stratified by Body Mass Index (BMI), the inverse association was evident in obese women (BMI ≥30 kg/m^2; RR 0.72, 95%CI 0.58–0.90) but not in non–obese women (BMI <30 kg/m^2) (RR 1.08, 95%CI 0.82–1.43).

3.6.2 Diabetes

Evidence summary

Evidence classification: Convincing.

There is convincing evidence of an association between personal history of diabetes[xv] and an increased risk of endometrial cancer. Risk estimates are higher from meta–analyses compared to pooled analyses. The increased risk has been estimated as 1.89 (95%CI 1.46–2.45) in one meta–analysis[167], although many studies have considerable bias and the magnitude of risk associated with diabetes independent of body fatness is likely to be smaller (e.g. RR 1.31, 95%CI 1.08–1.59)[168].

[xv] Type 1 or type 2 diabetes not specified in meta–analyses or pooled analyses but approximately 90% of all diabetes is type 2 diabetes

Worldwide, 10.8% of endometrial cancers are estimated to be attributable to diabetes [compared to 31.0% for high BMI].[169]

Background

Type 1 diabetes is an auto–immune condition in which the immune system is activated to destroy the cells in the pancreas which produce insulin. Type 1 diabetes is not linked to modifiable lifestyle factors. Type 2 is a long term metabolic disorder characterised by high blood sugar, insulin resistance and a relative lack of insulin (hyperinsulinemia). The major risk factors for type 2 diabetes are obesity and lack of physical activity, although genetic predisposition can also play a role. Type 2 diabetes represents approximately 90% of all cases of diabetes.

Hyperinsulinemia can decrease levels of sex–hormone binding globulin (SHBG). SHBG is a protein that binds and modulates the biological activity of oestrogens; thus, in patients with diabetes, levels of bioactive oestrogen may be increased. Elevated oestrogen levels promote the development of endometrial cancer.[14]

Recent evidence

Two pooled analyses[14, 62] and three meta–analyses[167, 170, 171] were identified for inclusion.

A pooled analysis by Cote et al. (2015)[62] of data from 7 cohort studies and 4 case–control studies that participate in the Epidemiology of Endometrial Cancer Consortium (E2C2)[xvi] reported that self–reported diabetes[xvii] was associated with similar increases in risk of endometrial cancer among black women (OR1.41, 95%CI: 1.07–1.87) and white women (OR 1.30, 95%CI 1.15–1.46) after adjustment for major confounders.[62]

A pooled analysis by Setiawan et al. (2013)[14] included 24 studies (10 cohort and 14 case–control studies) participating in the E2C2. Among 19 studies with diabetes data, there was a significant association between having a history of diabetes[xviii] and increased risk of endometrial cancer. The OR was 1.27 (95%CI 1.17–1.38) for type I endometrial cancer and 1.53 (95%CI 1.19–1.95) for type II endometrial cancer.

A meta–analysis by Liao et al. (2014)[167] included 29 cohort studies (17 prospective, 12 retrospective – 24 of which included endometrial cancer incidence data). Nineteen of the 29 studies included both type 1 and type 2 diabetes as the exposure. It was considered that there was considerable risk of bias in most of the included studies, particularly as often only patients hospitalised for diabetes were included and in some studies the response rate was very low; further, there was a considerable degree of methodological and clinical heterogeneity among the included studies, although relatively low statistical heterogeneity was observed among studies reporting RR and IRR as effect measures. The summary RR was 1.89 (95%CI 1.46–2.45).

[xvi] E2C2 is an international consortium formed in 2006 to provide a collaborative environment to address questions around endometrial cancer by pooling data from existing studies that would be underpowered in individual studies. To date, it includes data from more than 40 studies from the United States, Canada, Europe, Asia and Australia.
[xvii] Type 1 or 2 diabetes not specified
[xviii] Type 1 or 2 diabetes not specified

Two further meta–analyses by Starup–Linde et al. (2013) and Zhang et al. (2013) reported an increased risk of 1.81 (95%CI 1.63–2.01; 29 observational[xix] studies) and RR 1.92 (95%CI 1.23–3.01;15 cohort studies)/SIR 1.81(95%CI 1.38–2.37); respectively.[170,171]

The limitations of the evidence base were stressed by Tsilidis et al (2015)[172] in their umbrella review of meta–analyses of observational studies examining the validity of associations between type 2 diabetes and the incidence of endometrial cancer.

Luo et al (2014)[168] analysed data from the Women's Health Initiative including a total of 88,107 postmenopausal women with 11 years of follow–up (1,241 cases). Elevated risk was noted when combining diabetes diagnosed at baseline and during follow–up as a time–dependent exposure after adjusting for BMI (HR 1.31, 95%CI 1.08–1.59). Various analyses showed that the association may be affected by body weight, but some modest independent elevated risk remains.

3.6.3 Endometrial hyperplasia and polyps

Evidence summary

Evidence grading—Endometrial hyperplasia: Convincing (Atypical endometrial hyperplasia).

Evidence grading—Polyps: Convincing (postmenopausal women and women with abnormal uterine bleeding).

There is convincing evidence that endometrial hyperplasia is associated with an increased risk of endometrial cancer. Atypical hyperplasia, particularly complex hyperplasia with atypia, is associated with a higher risk of coexistence or progression to endometrial cancer compared with hyperplasia without atypia. Atypical hyperplasia is also considered a precursor of type I endometrial cancer. The risk of endometrial hyperplasia progressing to endometrial cancer is estimated to be between RR 8.74 (95%CI 6.66–11.47) and RR 29.22 (95%CI 13.24–64.51) depending on the classification system used.[173] Approximately 28% of women with untreated complex hyperplasia with atypia progress to endometrial cancer.[174] Up to 42% of women with atypical endometrial hyperplasia are found to have concurrent endometrial cancer diagnosed at the time of hysterectomy.[175, 176] The risk of progression of endometrial hyperplasia without atypia to endometrial cancer has not been well studied.

The rate of malignancy in women with endometrial polyps is low and is estimated as 2.73% (95%CI 2.57–2.91) in women who undergo surgical removal of lesions.[177] In women with endometrial polyps, the presence of abnormal bleeding or postmenopausal status is associated with a higher risk of endometrial cancer compared with women without bleeding (RR 1.97, 95%CI 1.24–3.14) or who are premenopausal (RR 3.86, 95%CI 2.92–5.11).[178]

Background

Endometrial hyperplasia is characterised by abnormal proliferation of endometrial glands resulting in a greater gland to stroma ratio compared with normal proliferative endometrium.

[xix] Included cross–sectional studies

Classification of endometrial hyperplasia has been a long–standing issue.[179] The World Health Organization (WHO, 2014) system classifies endometrial hyperplasia into two categories: hyperplasia without atypia and atypical hyperplasia. While hyperplasia without atypia is a non–neoplastic change (i.e. benign), atypical hyperplasia, also termed as endometrial intraepithelial neoplasm, is a premalignant lesion which exhibits many cellular and genetic changes associated with invasive carcinoma. The preceding 1994 WHO classification system categorised endometrial hyperplasia based on histological features in an attempt to stratify endometrial hyperplasia based on their potential for malignant transformation. Categories included simple hyperplasia without atypia, simple atypical hyperplasia, complex hyperplasia without atypia and complex atypical hyperplasia. The 1994 WHO system did not however reflect the dichotomous nature of endometrial hyperplasia. Endometrial intraepithelial neoplasia (EIN) is an alternative system to WHO criteria that was introduced in 2000, to diagnose benign and premalignant endometrial hyperplasia [179]. The EIN system is based on nuclear and architectural features of endometrial hyperplasia, which can be objectively assessed through a computerized morphometric analysis calculating a prognostic score, the D score. EIN system classifies endometrial hyperplasia as "benign" if D score ≥1, and "EIN" if D score <1.[173]

Atypical hyperplasia may progress to or coexist with endometrial cancer. However, it is sometimes difficult to distinguish a precursor lesion from endometrial cancer.[179] The risk of progression of endometrial hyperplasia to endometrial cancer depends on the nature of the lesion, which can be a benign reaction to an unopposed action of oestrogens, or a neoplastic premalignant process. The presence of nuclear atypia is the most important indicator of the risk of endometrial cancer in women with endometrial hyperplasia. Although atypical endometrial hyperplasia is the least common type of hyperplasia, it is the type most likely to progress to type 1 endometrial cancer.[180]

Similar to most cases of endometrial cancer, endometrial hyperplasia often results from exposure of the endometrium to continuous oestrogen unopposed by progesterone. Physiologically, oestrogen stimulates endometrial proliferation whereas progesterone inhibits endometrial proliferation and stimulates differentiation. Risk factors for endometrial hyperplasia are therefore similar to those for endometrial cancer.[181]

Endometrial polyps are localised overgrowths of endometrial glands and stroma that form a projection from the surface of the endometrium. Polyps are a common cause of abnormal uterine bleeding in both premenopausal and postmenopausal women. However, they may also be asymptomatic.[182] Abnormal uterine bleeding is the most common presenting symptom and occurs in 64–88% of women with polyps.[183] Most endometrial polyps are benign and spontaneous regression can occur. Malignant and premalignant atypical changes may be found within an endometrial polyp. However, endometrial polyps *per se* do not constitute a precursor lesion that carries a high risk of malignancy.[182]

Polyps are rarely diagnosed before menarche and their association with tamoxifen use suggests that oestrogen stimulation of the endometrium plays an important role in the development of endometrial polyps. Other proposed molecular mechanisms include overexpression of endometrial aromatase, and genetic mutations such as rearrangements in the high–mobility group (HMG) family of transcription factors.[178]

Recent evidence

Endometrial hyperplasia

Kurman et al. (1985)[184] retrospectively analysed data from 170 untreated patients diagnosed with endometrial hyperplasia on uterine curettage. Over a mean follow–up period of 13.4 years, 13 progressed to endometrial cancer. The endometrial cancer progression rates were reported as 1% (simple hyperplasia, without atypia), 3% (complex hyperplasia without atypia), 8% (simple atypical hyperplasia) and 29% (complex atypical hyperplasia), respectively. However the differences in progression rates between the four categories were not statistically significant due to the small sample size.

Lacey et al. (2008)[185] conducted a nested case–control study including 138 cases of endometrial hyperplasia who progressed to endometrial cancer at least 1 year after diagnosis (median 6.5 years) and 241 matched controls. Compared with women with disordered proliferative endometrium (as a referent), women with atypical hyperplasia had significantly increased carcinoma risk (RR 14, 95%CI 5–38) which was highest 1–5 years after atypical hyperplasia diagnosis (RR 48, 95%CI 8–294). In contrast, progression risks of simple hyperplasia and complex hyperplasia without atypia were much lower (RR 2.0, 95%CI 0.9–4.5) and (RR 2.8, 95%CI 1.0–7.9), respectively. In a subsequent analysis of the data by Lacey et al. (2010)[174], a diagnosis of non–atypical endometrial hyperplasia was associated with a cumulative risk of carcinoma of 1.2% (95%CI 0.6–1.9) after 4 years, 1.9% (95%CI 1.2–2.6) after 9 years and 4.6% (95%CI 3.3–5.8) after 19 years. For atypical hyperplasia, cumulative risk increased from 8.2% (95%CI 1.3–14.6) at 4 years, 12.4% (95%CI 3.0–20.8) at 9 years and 27.5% (95%CI 8.6–42.5) at 19 years after diagnosis of atypical hyperplasia.

A meta–analysis by Raffone et al. (2019)[173] assessed the risk of cancer progression of endometrial hyperplasia to endometrial cancer using the two classification systems for endometrial hyperplasia diagnosis, WHO 2014 and EIN, across 11 cohort studies and 1 case–control study. Endometrial hyperplasia included both premalignant and benign types of endometrial hyperplasia in the analysis. The WHO 2014 system showed a RR for progression of endometrial hyperplasia to endometrial cancer of 8.74 (95%CI 6.66–11.47; 10 studies) whereas using the EIN objective D score system the RR was 29.22 (95%CI 13.24–64.51; 6 studies). Subjective application of the EIN system showed an intermediate RR between WHO and D score of 19.37 (95%CI 5.86–64.01; 2 studies).

Coexistence of endometrial hyperplasia with endometrial cancer has also been demonstrated in the literature. Rakha et al. (2012)[175] included a total of 2,572 patients diagnosed with atypical endometrial hyperplasia on endometrial samples from 31 studies, in addition to an analysis of Institutional data. Thirty–seven per cent of women with a diagnosis of atypical endometrial hyperplasia on endometrial sampling were found to have endometrial cancer on subsequent biopsy or hysterectomy. There was a wide variation in the positive predictive value of atypical endometrial hyperplasia in detecting endometrial cancer (6% to 63%). This variation was caused not only by the differences among studies but also the degree of atypia, the type of subsequent intervention (biopsy vs. hysterectomy), and, importantly, the time period of diagnosis. In women with benign diagnosis (including hyperplasia without atypia), nearly 40% to 50% showed atypical hyperplasia with a potential risk of progressing to invasive carcinoma in 25% of cases.

In a multi–institutional prospective cohort study, which was included in the systematic review by Rakha et al. (2012)[175], Trimble et al. (2006)[176] reported that 42.6% of women who had a

diagnosis of atypical endometrial hyperplasia were diagnosed with concurrent endometrial cancer. The study analysed 289 women diagnosed with atypical endometrial hyperplasia who underwent hysterectomy and specimens reviewed by a panel of expert pathologists.

Semere et al. (2011)[186] estimated endometrial cancer outcomes among 177 diagnosed cases of EIN in women in a tertiary care multigroup practice who subsequently underwent hysterectomy. EIN was a high risk factor for malignancy, with 35.7% (56 of 157, 95%CI 28.2–43.7%) overall having carcinoma at initial diagnosis or during follow–up. Among women diagnosed with EIN 15% (26 of 177, 95%CI 9.8–20.8%) had concurrent cancer in the presenting biopsy, 19% (25 of 131, 95%CI 12.7–26.9%) had cancer develop within 1 year, and an additional 4% (5 of 131, 95%CI 1.2–8.7%) had cancer develop after 1 year.

Most recently, Travaglino et al. (2019)[187] assessed the risk of coexistent endometrial cancer with endometrial hyperplasia using the WHO 2014 and EIN classification systems. Sixteen cohort studies and three case–control studies, assessing 2582 endometrial hyperplasia cases, were included in the analysis. The risk of endometrial cancer coexistence with endometrial hyperplasia using the WHO criteria was OR 11.15 (95%CI 7.65–16.24; 9 studies). The subjective EIN system showed a similar OR of 11.85 (95%CI 4.91–28.62; 4 studies).

Older age (40–59 years, OR 3.07, 95%CI 1.18–7.97; ≥60 years, OR 6.65, 95%CI 1.75–25.3), obesity (BMI ≥35 kg/m^2, OR 2.32, 95%CI 1.09–4.93), diabetes mellitus (OR 2.51, 95%CI 1.16–5.39) and complex atypical endometrial hyperplasia (OR 9.01, 95%CI 1.09–74.6) are the strongest predictors of concurrent endometrial carcinoma among women with endometrial hyperplasia.[188]

Polyps

Lee et al. (2010)[178] conducted a systematic review and meta–analysis of 17 observational studies including over 10,572 women with endometrial polyps who underwent polypectomy. The incidence of polyps that were malignant (defined as polyps with either complex atypical hyperplasia or endometrial cancer) was significantly higher in postmenopausal compared with premenopausal women (5.42% versus 1.70%, RR 3.86, 95%CI 2.92–5.11). Women with abnormal uterine bleeding and polyps had significantly higher rates of malignant polyps compared with those without bleeding (4.15% versus 2.16%, RR 1.97, 95%CI 1.24–3.14). More postmenopausal women with abnormal bleeding and endometrial polyps had a malignant polyp than asymptomatic postmenopausal women (4.47% versus 1.51%, RR 3.36, 95%CI 1.45–7.80). Postmenopausal status and abnormal bleeding are also associated with an increased risk of endometrial cancer without the presence of polyps. The data regarding polyp size and risk of malignancy were not amenable to meta–analysis because of the differing units of measurement; however, the data suggested that polyp size does not independently predict risk of malignancy.

Similar results were reported by a more recent meta–analysis by Uglietti et al. (2019)[177] which included additional studies to those analysed by Lee et al. (2010)[178]. A total of 51 studies reporting data on 35,345 women with endometrial polyps who underwent surgical removal of lesions were reviewed. The prevalence of malignant polyps was 2.73% (95%CI 2.57–2.91) with very high heterogeneity among studies. The rates were significantly lower for premenopausal (1.12%) compared to postmenopausal women (4.93%). The risk of malignancy was higher among symptomatic (5.14%) compared to asymptomatic women (1.89%). A higher rate of malignant polyps was observed in prospective studies (pooled estimate 5.88, 95%CI 4.06–7.97; 10 studies) than retrospective studies (pooled estimate 2.94, 95%CI 2.24–3.71; 41 studies).

3.6.4 Endometriosis

Evidence summary

Evidence classification: Inconclusive.

The evidence for any association between endometriosis and risk of endometrial cancer is inconclusive. Findings from two recent meta–analyses involving large numbers of studies are inconsistent and the need for stronger-quality studies has been identified.

Background

Endometriosis is a condition in which the endometrium grows outside of the uterus and causes pain and infertility. While considered a benign gynaecological disease, endometriosis shows similar characteristics to malignancy including uncontrolled growth, inhibition of apoptosis, invasion and angiogenesis. Endometriosis is classified as a 'tumour–like lesion' by the World Health Organization.[189] Endometriosis is considered an oestrogen–dependent chronic inflammatory condition and its relationship with cancer could either be a marker of certain underlying biologic factors such as unbalanced oestrogen metabolism or be linked to complex immune–mediated mechanisms.[190]

Recent evidence

A meta–analysis by Li et al. (2019)[189] found no association between endometriosis and risk of endometrial cancer (RR 1.176; 95%CI 0.878–1.575; 9 studies with high heterogeneity). Of the included studies in the meta–analysis, three reported an increased risk of endometrial cancer, one reported a decreased risk and the other five studies reported no association. Two of the included studies, a case–cohort study using the Danish hospital discharge database (1398 cases) [Brinton et al. 2005][191] and an Australian case–control study (1399 cases) [Rowlands et al. 2011][192], reported a suggested increased risk that was strongest in the first year after endometriosis diagnosis, indicating a potential for increased detection of endometrial cancer among women with endometriosis, rather than a true association.

A meta–analysis by Gandini et al. (2019)[190] included 16 studies (11 cohort, 4 case–control and 1 cross–sectional); three of these studies were included in the analysis by Li et al. (2019)[189] and five were published in 2018. A positive association between endometriosis and risk of endometrial cancer was reported (RR 1.38, 95%CI 1.10–1.74), although there was a large between–studies heterogeneity. Further, only three of the 11 prospective studies included in the meta–analysis showed a significant positive association and one of the other studies that showed a positive association was the cross–sectional study[xx]. The authors noted the need for properly designed cohort studies with clinical confirmation of endometriosis as the studies were limited in this, and other, regards.

In a population–based study of 2,882,847 women registered in the Swedish Multi–Generation Register, endometrial cancer incidence was significantly higher in women diagnosed with

[xx] Cross–sectional studies are very low quality studies and cannot be used to establish causal associations. This study type is not generally included in epidemiological analyses.

either infertility (HR 1.21, 95%CI 1.07–1.38) or ovulatory disturbances (HR 1.45, 95%CI 1.12–1.88), but not in women diagnosed with endometriosis (HR 0.94, 95%CI 0.76–1.17).[193] Lundberg et al. (2019)[193] reported that incidence of endometrial cancer was also not higher among women diagnosed with both endometriosis and infertility (HR 0.87, 95%CI 0.58–1.30).

3.6.5 Gall bladder disease

Evidence summary

Evidence classification: Inconclusive.

The evidence for an association between gall bladder disease and risk of endometrial cancer is inconclusive. There is a limited amount of low level evidence available, and findings are suggestive of no association. There is no plausible biological mechanism.

Background

The gallbladder is a small organ that stores and releases bile into the small intestine to aid in digestion. Cholelithiasis, also known as gallstones, is the most common form of gallbladder disease. Gallstones result from buildup of solidified bile and cholesterol in the gallbladder which can block bile flow. Cholecystectomy is the surgical removal of the gallbladder.

Changes in bile release due to cholelithiasis may modulate the risk of digestive tract neoplasms. There is no plausible biological mechanism for an association between gallbladder disease and risk of endometrial cancer.[194]

Recent evidence

One pooled analysis was identified for inclusion.[194]

The analysis by Tavani et al. (2012)[194] examined the relationship between cholelithiasis and cancer risk across a network of case–control studies in Italy. Data were available for only one case–control study with 1,458 cases and 3,822 matched controls, and there was no association between having a history of cholelithiasis and risk of endometrial cancer (OR 0.92, 95%CI 0.76–1.12).

Tavani et al. (2012)[194] indicated that findings across three other studies were inconsistent. These studies were: a retrospective (record linkage) cohort study by Johansen et al. (1996)[195](RR 1.10, 95%CI 0.9–1.3, for patients with gall stones compared with reference cohort); a case–control study by Morimoto et al. (2006)[196] (OR 1.5, 95%CI 1.1–2.0, for never versus ever having had a cholecystectomy—relationship only apparent among never hormone users—and no association for ever versus never having gall stones, OR 1.2, 95%CI 0.9–1.5); and a retrospective (record–linkage) cohort study by Goldacre et al. (2005)[197] (RR for uterine cancer 1.13, 95%CI 0.91–1.38, among women having had a cholecystectomy compared with a reference cohort).

3.6.6 Hypertension

Evidence summary

Evidence classification: Inconclusive.

The evidence for an association between hypertension (high blood pressure) and risk of endometrial cancer is inconclusive. Findings across meta–analyses compared to a pooled analysis are inconsistent and most studies have not adjusted for multiple confounders. The increased risk of endometrial cancer reported in some studies may be associated with comorbid conditions such as obesity and diabetes which are independently associated with risk of endometrial cancer.

Background

Hypertension or high blood pressure is a medical condition that increases risk of cardiovascular disease. A biological mechanism for an association between hypertension and endometrial cancer is unclear. It has been suggested that long–term hypertension may lead to cellular senescence and inhibition of apoptosis. It has also been suggested that medications used for the treatment of hypertension could increase cancer risk.[108]

Recent evidence

Four studies were identified for inclusion, one was a pooled analysis[62] and three were meta–analyses[108, 198, 199].

In a meta–analysis by Seretis et al. (2019)[199], there was a significant association between hypertension and risk of endometrial cancer among nine prospective studies (RR 1.37, 95%CI 1.14–1.64) but with substantial heterogeneity. Seven studies adjusted at least for age (RR 1.44, 95%CI 1.17–1.76) but there was no association among two studies with multivariate adjustment (RR 1.05, 95%CI 0.83–1.34). When 13 case–control studies were meta–analysed together with the prospective studies, a significant association was found (RR 1.58, 95%CI 1.35–1.85; high heterogeneity). The authors indicated that the lack of multivariate adjustment in the majority of studies raises serious concerns over the validity of the estimated associations.

The meta–analysis by Aune et al. (2017)[108] included 25 studies (6 cohort and 19 case–control studies) and reported a significant association between hypertension and risk of endometrial cancer (RR 1.61, 95%CI 1.41–1.85). The magnitude of the increased risk was smaller when analysis was limited to the prospective cohort studies (RR 1.32, 95%CI 1.12–1.56). Heterogeneity was higher when studies were stratified by adjustment for major confounding factors, with weaker but still generally significant associations among studies with such adjustments; the exception was an analysis which adjusted for physical activity (RR 1.27, 95%CI 0.88–1.81; 3 studies). The exposure data in the majority of studies was from self–report. The authors concluded that further studies with more comprehensive adjustments for confounders are warranted to clarify the association.

A preceding meta–analysis conducted by Esposito et al. (2014)[198] focusing on metabolic syndrome also showed an increased risk of endometrial cancer associated with hypertension

(RR 1.81, 95%CI 1.08–3.03). This analysis was based on only five studies (1 cohort and 4 case–control studies; 2 studies of which were included by Aune et al. 2017[108]).

A pooled analysis by Cote et al. (2015)[62] based on individual patient data (IPD) from eleven studies (7 cohort and 4 case–control studies) participating in the Epidemiology of Endometrial Cancer Consortium (E2C2)[xxi] showed no association between history of hypertension and risk of endometrial cancer in black women (OR 0.88, 95%CI 0.66–1.17) or in white women (OR 0.99, 95%CI 0.90–1.08). Pooled analyses of individual patient data are generally better able to adjust for confounders than meta–analyses.

3.6.7 Metformin

Evidence summary

Evidence grading: Inconclusive.

The evidence for an association between metformin use and risk of endometrial cancer is inconclusive. Findings across studies are inconsistent and the studies are limited in quality, many with a high risk of bias.

Background

Metformin belongs to the 'biguanides' class of medicines and is used for treating patients with Type 2 diabetes. Metformin reduces glucose production in the liver and enhances sensitivity of body's tissues to insulin.

It is proposed that the reduced insulin and insulin–like growth factor 1 (IGF–1) levels associated with metformin use could decrease the risk of endometrial cancer as insulin and IGF–1 are believed to exert direct effects on the activation of cellular pathways of tumour cells.[200]

Recent evidence

Four recent meta–analyses were identified for inclusion.[200-203] All meta–analyses included studies with patients with type 2 diabetes as the population group and compared 'metformin use' with 'non–metformin use'. None of the meta–analyses examined dose or duration of metformin use.

Tian et al. (2019)[202] included six studies (2 retrospective cohort and 4 case–control studies; 5 of which were included in the meta–analysis by Chu et al. (2018)[201]) and showed no significant association between metformin use versus non–use and risk of endometrial cancer among patients with diabetes (unadjusted OR 1.15, 95%CI 0.70–1.88). There was considerable heterogeneity between studies which was mainly due to one study by Tseng (2015)[204] – a very large retrospective cohort study. Exclusion of this study resulted in a

[xxi] E2C2 is an international consortium formed in 2006 to provide a collaborative environment to address questions around endometrial cancer by pooling data from existing studies that would be underpowered in individual studies. To date, it includes data from more than 40 studies from the United States, Canada, Europe, Asia and Australia.

significantly increased risk of endometrial cancer associated with metformin use (unadjusted OR 1.29; 95%CI 1.16–1.44).

The analysis by Chu et al. (2018)[201] included seven studies (4 cohort studies and 3 case–control studies; 5 of which were included in the meta–analysis by Tian et al. (2019)[202], including the study by Tseng (2015)[204]), and found no association between metformin use versus non–use and risk of endometrial cancer (OR 1.05, 95%CI 0.82–1.35). Metformin use was not associated with risk of endometrial cancer compared to use of other antidiabetic therapies (OR 0.99, 95%CI 0.78–1.26).

A meta–analysis by Tang et al. (2017)[200] included five studies (3 cohort and 2 case–control studies), all of which were included in the meta–analysis by Chu et al. (2018)[201]. This analysis showed a significantly decreased risk of endometrial cancer in women with diabetes who ever used metformin compared to those who never used metformin (OR 0.87, 95%CI 0.80–0.95).

A meta–analysis by Wen et al. (2019)[203] included only four of the seven studies included by Chu et al. (2018)[201] and showed no association between metformin use and risk of endometrial cancer (RR 0.71, 95%CI 0.29–1.74 and RR 0.89, 95%CI 0.27–2.95; for subgroup analysis for number of persons and subgroup analysis for person years, respectively). It was noted that in some of the primary studies non–metformin users may have been taking other antidiabetic medication, thereby leading to an overestimate of the effect of metformin use versus non–use.

3.6.8 Oral bisphosphonates

Evidence summary

Evidence classification: Probable.

Use of oral bisphosphonates for at least one year is probably associated with a decreased risk of endometrial cancer.

Meta–analyses of cohort, nested case–control and case–control studies show a decreased risk of endometrial cancer associated with bisphosphonates use but only among women who have used them for longer than one year and among postmenopausal women. The decreased risk associated with at least one year of use has been estimated as 0.57 (95%CI 0.35–0.93[xxii]).[205] There is evidence of a dose–response relationship for use beyond one–year.

Background

Bisphosphonates are a class of medicines used to treat osteoporosis. Several potential mechanisms for a protective effect of use of bisphosphonates on risk of endometrial cancer have been proposed. *In vitro*, bisphosphonates can reduce metastasis potential and colony formation ability of endometrial cell lines. Bisphosphonates possess inhibitory effects on the proliferation of cancer cell lines by binding to human epidermal growth factor receptors

[xxii] The confidence intervals on this estimate are wide indicating a lack of confidence in the magnitude of risk

resulting in the disruption of metabolic pathways essential for cancer cell growth, motility, invasion, and survival. Furthermore, bisphosphonates may also exert indirect anti–tumour effects by modulating the immune system.[206]

Recent evidence

Four studies were identified for inclusion, one was a pooled analysis[207] and three were meta–analyses[205, 206, 208].

Vinogradova et al. (2013)[207] conducted an analysis of individual patient data from a series of population–based nested case–control studies based on medical records from the two largest UK primary care databases (91,556 and 88,845 cases). Use of bisphosphonates was not associated with risk of uterine cancer (OR 1.00, 95%CI 0.81–1.24), however this analysis did not stratify by duration of use.

The meta–analysis by Ou et al. (2016)[206] included 4 cohort studies, the pooled analysis of the two nested case–control studies by Vinogradova et al. (2013)[207] and two case–control studies. 'Any' versus 'never' use of a bisphosphonate was associated with a decreased risk of endometrial cancer (RR 0.75, 95%CI 0.60–0.94). Subgroup analyses indicated that use of a bisphosphonate for more than one year was associated with a decreased risk of endometrial cancer. The decrease in risk was larger with longer duration of bisphosphonate use (RR ≥1 to 3 years vs. none 0.58, 95%CI 0.47–0.72; RR ≥3 years vs. none 0.44, 95%CI 0.28–0.70).

Very similar findings are reported in a more recent meta–analysis by Zhang et al. (2018)[205], which included the same studies as Ou et al. (2016)[206] except for one of the cohort studies with very wide confidence intervals by Lee et al. (2012)[209]. Any use of bisphosphonates was associated with a decreased risk of endometrial cancer (RR 0.73, 95%CI 0.58–0.93). Subgroup analyses showed the inverse association only in postmenopausal women (RR 0.53, 95%CI 0.34–0.93) and in those who had received bisphosphonates for more than 1 year (RR 0.57, 95%CI 0.35–0.93).

The meta–analysis by Deng et al. (2018)[208] included three out of the four cohort studies (157,872 osteoporosis patients) included by Ou et al. (2016)[206], including the study by Lee et al. (2012)[209], and showed that oral bisphosphonate use was associated with a decreased risk of endometrial cancer among postmenopausal women with osteoporosis (HR 0.79, 95%CI 0.64–0.96).

3.6.9 Paracetamol (acetaminophen)

Evidence summary

Evidence classification: Evidence of no association.

There is evidence of no association between paracetamol use and risk of endometrial cancer. A meta–analysis[210] and a pooled analysis[162] of cohort studies and case–control studies have shown that using paracetamol (ever or regular use) is not associated with risk of endometrial cancer. There is no evidence of a dose–response association and there is no clear biologically plausible mechanism for an association.

Background

Paracetamol is a medication that is used to treat pain and fever. The mechanism of action of paracetamol is not completely understood but is thought to involve endogenous cannabinoid system modulation.[211]

Increasing evidence suggests that inflammation and the COX pathway are involved in endometrial carcinogenesis. *In vitro* studies suggest that COX–2 expression is elevated in endometrial cancer cells compared with normal endometrial cells, and inhibition of the enzyme reduces proliferation of cancer cells. Recent experimental studies have found that paracetamol does not possess COX–2 inhibitory properties and that the drug has limited evidence of chemopreventive effects.[210]

Recent evidence

Two studies were identified for inclusion, a meta–analysis[210] and a pooled analysis[162].

The meta–analysis by Ding et al. (2017)[210] included seven studies (4 cohort and 3 case–control studies). There was no association between ever use of paracetamol versus never use of paracetamol and risk of endometrial cancer (RR 1.02, 95%CI 0.93–1.13; 7 studies). There was similarly no association when the analysis was restricted to the prospective cohort studies (RR 1.00, 95%CI 0.90–1.12). Secondary analyses by subgroups (including number of cases, exposure measurement and geographic location) and variables adjusted for (including age, BMI, parity, oral contraceptive use and MHT use) also showed no association. Further, no association was found in women in the higher frequency or longer duration of paracetamol use groups compared to those in the lower frequency or shorter duration of use groups (RR 0.88, 95%CI 0.70–1.11, 6 cohort/case–control studies; and RR 0.83, 95%CI 0.67–1.04, 3 cohort studies; respectively).

Webb et al. (2019)[162] conducted a pooled analysis of seven studies (4 cohort and 3 case–control studies) which assessed the risk of endometrial cancer associated with paracetamol use and which are part of the Epidemiology of Endometrial Cancer Consortium. Four of the seven studies (1 cohort and 3 case–control studies) were included in the meta–analysis by Ding et al. (2017)[210]. The individual pooled data (IPD) analysis showed no association between regular use of acetaminophen and risk of endometrial cancer (OR 0.98, 95%CI 0.87–1.10). Stratification by BMI suggested an inverse association among overweight women (OR 0.79, 95%CI 0.64–0.96) but no association among normal weight (OR 1.10, 95%CI 0.91–1.33) or obese women (OR 1.04, 95%CI 0.86–1.24). Stratification by other variables including parity, contraceptive use, MHT use, race, and tumour type, did not affect the lack of association.

3.6.10 Selective oestrogen receptor modulators

Evidence summary

Evidence classification — tamoxifen: Convincing.

Evidence classification—raloxifene: Evidence of no association.

There is convincing evidence that use of tamoxifen, whether given as adjuvant therapy for women with breast cancer or as risk–reducing medication in women at high risk of breast cancer, is associated with an increased risk of endometrial cancer.

The increased risk of endometrial cancer associated with tamoxifen therapy compared with placebo among women at high risk of breast cancer has been estimated as RR 2.26 (95%CI 1.52–3.38).[212] The increased risk was observed only among women aged 50 years or older, and not among women aged less than 50 years in two of the randomised controlled chemoprevention trials.

Risk of endometrial cancer is estimated to be approximately two–fold higher for extended adjuvant therapy using tamoxifen compared to standard 5–year tamoxifen therapy. Use of aromatase inhibitors is associated with a lower risk of endometrial cancer than tamoxifen therapy. Also, sequencing therapy with aromatase inhibitors, i.e. using aromatase inhibitors as an alternative to continued treatment with tamoxifen, is associated with a lower risk of endometrial cancer compared to tamoxifen–only therapy.

There is evidence from several randomised controlled trials, and other studies, of no association between use of raloxifene as a risk–reducing medication among women at high risk of breast cancer and risk of endometrial cancer. Use of raloxifene compared to use of tamoxifen is associated with a lower risk of endometrial cancer.

Background

Women considered to be at high risk of breast cancer, for example due to a family history or BRCA1/BRCA2 status, are typically offered endocrine therapy with a selective oestrogen receptor modulator (SERM) such as tamoxifen or raloxifene, to reduce their risk of breast cancer. This is often termed 'chemoprevention' or 'risk–reducing medication'. Tamoxifen is offered to premenopausal and postmenopausal women. Raloxifene is only considered for postmenopausal women. Additionally, tamoxifen is used for the treatment of hormone–receptor positive breast cancer, reducing the chances of the cancer spreading and the chances of recurrence. Raloxifene is also used in the prevention and treatment of osteoporosis in postmenopausal women. Aromatase inhibitors such as anastrazole and letrozole are a different type of hormone therapy used in the treatment of oestrogen–receptor positive breast cancer in postmenopausal women, and are used as an alternative to tamoxifen or in sequence after tamoxifen.

SERMs attach to the oestrogen–receptor in breast cells, blocking the oestrogen from attachment such that the cell does not receive oestrogen's signals to grown and multiply. Tamoxifen is oestrogenic in bone tissue and the uterus, while raloxifene is oestrogenic in bone and anti–oestrogenic in the uterus. In addition, tamoxifen regulates target genes which despite being different to that of oestrogen, exhibit overlapping effects enhancing endometrial cell proliferation and cancer progression.[213] Raloxifene is similar to tamoxifen in imparting anti–oestrogenic effects in the breast, however it does not share the pro–oestrogenic effects of tamoxifen on the endometrium.[214] Aromatase inhibitors decrease circulating oestrogen by preventing the aromatase enzyme from converting androgen into oestrogen.

IARC

The International Agency for Research on Cancer (IARC 2012, Volume 100A)[84] concluded that there is sufficient evidence in humans for the carcinogenicity of tamoxifen. Tamoxifen is considered carcinogenic to humans (Group 1) and causes cancer of the endometrium.

The effect of tamoxifen in increasing risk of endometrial cancer among women with breast cancer has been reported in nine cohort studies, four case–control studies, five randomised controlled treatment trials (RCTs) and one major chemoprevention trial; the majority of these in meta–analyses, though there were four separate reports from individual trials. The data are largely consistent in showing that tamoxifen, whether given as adjuvant therapy for women with breast cancer or for chemoprevention in women at high risk of breast cancer, increases the risk of endometrial cancer.

Recent evidence

Primary prevention of breast cancer among high–risk women

Tamoxifen versus placebo

Three large randomised controlled trials (RCTs) examining the effectiveness of tamoxifen in the prevention of breast cancer among women at high risk, have also reported on the incidence of endometrial cancer among treatment and placebo groups.

Individual study findings are:

- National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (P1) [NSABP P–1]
    - RR 3.28 (95%CI 1.87–6.03)[215] [difference only significant in women aged older than 49 years]
    - RR 2.46 (95%CI 1.35–4.48)[216]
- International Breast cancer Intervention Study [IBIS–I]:
    - RR 1.45 (95%CI 0.79–2.71)[217] [extended long–term follow–up]
    - RR 1.55 (95%CI 0.68–3.65)[218] [long–term follow–up]
- Royal Marsden Prevention Trial:
    - RR 2.59 (95%CI 0.86–9.30)[219].

Three meta–analyses have analysed data from these RCTs.[212, 220, 221]

The most recent meta–analysis by Mocellin et al. (2019)[212] included findings from the longer–term follow–up of the NSABP P–1[215] and IBIS–I[217], and from the Royal Marsden trial[219], and showed that tamoxifen significantly increased the risk of endometrial cancer compared with placebo (RR 2.26, 95%CI 1.52–3.38; high–certainty evidence).

A meta–analysis by Nelson et al. (2013)[220] of the earlier findings of the NSABP P–1 and the IBIS–1, as well as from the Royal Marsden trial (as reported by Fisher et al. (1998)[216], Cuzick et al. (2007)[218] and Powles et al. (2007)[219]), also showed a significantly increased risk of endometrial cancer with tamoxifen use compared to placebo (RR 2.13, 95%CI 1.36–3.32).

Meta–analysis by Iqbal et al. (2012)[221] of the findings from the two trials which separated outcome data by age (NSABP P–1 and IBIS–1), showed that women at high risk of breast cancer aged 50 years or older receiving tamoxifen for primary prevention of breast cancer

were at increased risk of endometrial cancer compared to those receiving placebo (RR 3.32, 95%CI 1.95–5.67), whereas there was no difference among women aged less than 50 years (RR 1.19, 95%CI 0.53–2.65).

Raloxifene versus placebo

Several randomised controlled trials (RCTs) designed to investigate impact of the use of raloxifene compared to placebo on other health outcomes, have also been examined with respect to risk of endometrial cancer. As these RCTs were not designed to assess endometrial cancer safety, they could have been underpowered to detect a difference in effect between raloxifene and placebo.

The MORE (Multiple Outcomes of Raloxifene Evaluation) study was a RCT designed to evaluate the effect of raloxifene on risk of breast cancer in 7,705 postmenopausal women. Cummings et al. (1999)[222] showed that, compared to placebo, use of daily raloxifene treatment over a median follow–up of 40 months was not associated with risk of endometrial cancer (RR 0.8, 95%CI 0.2–2.7). This association was reported as RR 0.9 (95%CI 0.3–2.7) from an analysis of data from the same study in the article by Grady et al. (2004)[223]. Similarly, in the RUTH (Raloxifene Use for The Heart) trial which assessed effects of raloxifene on cardiovascular events and breast cancer and included 10,101 postmenopausal women followed for a median of 5.6 years, Barrett–Connor et al. (2006)[224] reported that the incidence of endometrial cancer among those who took raloxifene was not significantly different from placebo (0.5% versus 0.4%, respectively).

Martino et al. (2005)[225] analysed the safety of raloxifene using 8–year follow–up data from 4,011 women participating in the MORE and CORE (Continuing Outcomes Relevant to Evista) trials. Frequency of other cancers (excluding breast cancer) among patients who received raloxifene for up to 8 years was significantly reduced compared to placebo (4.6% vs. 6.3%, respectively). There was no significant difference in the incidence of uterine cancer[xxiii] (0.32% raloxifene vs. 0.39% placebo) or endometrial hyperplasia (0.37% raloxifene vs. 0.29% placebo), although the frequency of benign uterine polyps was significantly increased (3.2% raloxifene vs. 1.9% placebo).

An earlier RCT reported on by Delmas et al. (1997)[226] investigated the effects of raloxifene on bone mineral density and serum lipid profiles, as well as safety with regards to the endometrium, in 601 postmenopausal women following a 2–year treatment. Compared to placebo, raloxifene treatment did not stimulate the endometrium as evidenced by a lack of difference in endometrial thickness.

In a more recent population–based case–control study, DeMichele et al. (2008)[214] assessed the impact of raloxifene on endometrial cancer risk. Analysis was of 547 cases and 1,410 controls of which 3.3% and 6.6% had taken raloxifene, respectively. Compared with non–SERM users, raloxifene use for less than 3 years was associated with a decreased risk of endometrial cancer (OR 0.41; 95%CI 0.21–0.80), and no association was observed for 3 or more years of use (OR 0.78; 95%CI 0.31–1.95).

[xxiii] Eleven uterine cancers across treatment and placebo groups comprised 10 endometrial cancers and one uterine cancer

Tamoxifen versus raloxifene

The STAR (Study of Tamoxifen and Raloxifene) P–2 trial (which was a second protocol of the NSABP) directly compared tamoxifen with raloxifene in 19,747 healthy postmenopausal women at an increased risk for development of breast cancer and has been reported on by Vogel et al. (2010)[227] and Runowicz et al. (2011)[228]. With 47 months of follow–up, there was a non–significant decreased risk of endometrial cancer in the raloxifene compared to tamoxifen group. After a median follow–up of 81 months, this difference was significant (RR 0.55, 95%CI 0.36–0.83). This equates to an increased risk of endometrial cancer associated with tamoxifen use compared to raloxifene use of RR 1.82 (95%CI 1.20–2.78).

Aromatase inhibitors versus placebo

The IBIS–II study investigated the efficacy and safety of the aromatase inhibitor anastrozole for the prevention of breast cancer compared with placebo. Cuzick et al (2014)[229] reported that, among 3864 women who underwent randomisation, there were 3 cases of endometrial cancer in the anastrozole group and 5 cases of endometrial cancer in the placebo group (RR 0.61, 95%CI 0.15–2.54) after a median of five years of follow–up.

Adjuvant therapy for women with breast cancer

Tamoxifen

Staley et al. (2012)[230] reported an increased risk of endometrial cancer in women with Ductal carcinoma in situ (DCIS) treated with tamoxifen compared with placebo (RR 2.33, 95%CI 0.61–8.99).

Al Mubarak et al. (2014)[231] conducted a meta–analysis of five RCTs and showed that extended adjuvant tamoxifen use was associated with an increased risk of endometrial carcinoma compared to use for 5 years (OR 2.06, 95%CI 1.65–2.58). Fleming et al. (2018)[232] analysed data from four RCTs included by Al Mubarak et al. (2014)[231] and also showed that extended adjuvant tamoxifen therapy was associated with an increased risk of endometrial cancer (RR 2.29; 95%CI 1.60–3.28) with cumulative risk of endometrial cancer increasing from 1.5% to 3.2% with extended therapy compared with the standard 5 years of tamoxifen.

Aromatase inhibitors vs. tamoxifen

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG, 2015)[233] examined the use of aromatase inhibitors and tamoxifen therapies among postmenopausal women with oestrogen–receptor–positive early breast cancer. Based on an analysis of pooled data from nine RCTs, use of tamoxifen resulted in a higher incidence of endometrial cancers compared to use of aromatase inhibitors (10–year incidence 1.2% vs.0.4%; RR 3.03, 95%CI 1.96–4.76[xxiv]). The absolute excess risk of endometrial cancer with tamoxifen compared to aromatase inhibitors was 0.7% (95%CI 0.5–0.9) at ages 55–69 years and 1.4% (95%CI 0.5–2.4) at older ages.

The EBCTCG pooled analysis included data from the single RCT reported on by Rydén et al. (2016)[234], which showed that use of tamoxifen plus aromatase inhibitors compared with aromatase inhibitors alone was associated with an increased risk of endometrial cancer (OR

[xxiv] Converted from comparison between aromatase inhibitors vs. tamoxifen reported as: RR 0.33 (95%CI 0.2–0.51).

2.45, 95%CI 1.02–5.92). Similar results were reported in the meta–analysis by Aydiner (2013)[235] which included a subset of the RCTs included in the EBCTCG pooled analysis. This meta–analysis showed that monotherapy with aromatase inhibitors was associated with a lower risk of endometrial cancer compared with use of tamoxifen (OR 0.26, 95%CI 0.13–0.49). Sequencing therapy, that is using aromatase inhibitors as an alternative to continued treatment with tamoxifen, was also found to confer lower endometrial cancer risk compared with tamoxifen therapy (OR 0.31, 95%CI 0.13–0.72).

Chlebowski et al. (2015)[236] examined the effect of different endocrine therapies – aromatase inhibitors, tamoxifen, switching from tamoxifen to aromatase inhibitors, or none – among a cohort of 17,064 women diagnosed with hormone receptor positive breast cancer in a group practice health plan in the US. Endometrial cancer incidence, obtained from the SEER tumour registry, was 48% lower in the aromatase inhibitor only versus tamoxifen group (HR 0.52, 95%CI 0.31–0.87). Endometrial cancer incidence was 29% lower in the aromatase inhibitor only versus no endocrine therapy group (HR 0.71, 95%CI 0.37–1.35) and was 33% lower in the switching group (tamoxifen to aromatase inhibitor) versus tamoxifen only group (HR 0.67, 95%CI 0.42–1.06), but neither difference was statistically significant.

3.6.11 Statins

Evidence summary

Evidence classification: Inconclusive.

The evidence for an association between statin use and risk of endometrial cancer is inconclusive. Meta–analyses of randomised controlled trials and observational studies report a high risk of bias in the available studies, and lack of an association.

Background

Statins are a class of medicines used to treat hypercholesterolaemia. Statins block the 3–Hydroxy–3–methylglutaryl–coenzyme A (HMG–CoA) reductase, the enzyme required for conversion of HMG–CoA to the cholesterol precursor mevalonic acid.

Potential preventive effects of statins against cancer have been related to their mechanism of action which involves inhibition of the rate–limiting enzyme in cholesterol synthesis pathway. It has been suggested that rapidly proliferating cancers require a high uptake of extracellular cholesterol. A reduction in cholesterol levels may limit cancer cell proliferation, growth and metastasis. Experimental evidence suggests that statins inhibit intracellular signaling pathways critical for proliferation, invasion and metastasis of cancer cells.[237]

Recent evidence

Two meta–analyses[237, 238] and one prospective cohort study[239] were identified for inclusion. Both meta–analyses included two randomised controlled trials that were not designed primarily for examination of cancer outcomes.

In the meta–analysis by Liu et al. (2014)[237], statin use was associated with a non–significant decrease in risk of gynaecologic cancers (RR 0.89; 95%CI 0.78–1.01). Stratified analyses based

on ten studies (2 RCTs, 4 cohort studies and 4 case–control studies) with 9,957 cases revealed no association between any use of statins and risk of endometrial cancer (RR 0.90, 95%CI 0.75–1.07; 10 studies) nor between long–term statin use (>5 years) and risk of endometrial cancer (RR 0.69; 95%CI 0.44–1.10; 5 studies).

The more recent meta–analysis by Yang et al. (2017)[238] also included ten studies, nine of which were included in the meta–analysis by Liu et al. (2014)[237] plus an additional case–control study (2 RCTs, 3 cohort studies and 5 case–control studies). The combined analysis of all included studies showed no association between statin use and risk of endometrial cancer (RR 0.94, 95%CI, 0.82–1.07). Analysis by study type did not affect the findings: the RR for the two RCTs was 0.72 (95%CI 0.19–2.67) and among non–randomised studies was 0.94 (95%CI 0.82–1.07).

Desai et al. (2018)[239] analysed data from the Women's Health Initiative (WHI), which is considered the largest multicentre longitudinal study of postmenopausal women in the United States. Among 161,808 women aged 50–79 years there were 1,377 endometrial cancer cases. Statin use at baseline (7.5% of women) was associated with a significantly decreased risk of endometrial cancer compared to non–users (HR 0.74, 95%CI 0.59–0.94). However in the time–dependent analysis which took into account statin use over a longer period of time (up to 9 years of use; 25% of women users), overall statin use was not associated with risk of endometrial cancer (HR 0.91, 95%CI 0.76–1.08).

3.6.12 Stress

Evidence summary

Evidence grading: Inconclusive

The evidence for any association between stress and risk of endometrial cancer is inconclusive. Only one cohort study was identified.

Background

Several mechanisms have been suggested for an association between stress and decreased risk of endometrial cancer. Stress may decrease gonadal synthesis of oestrogens and alter the sensitivity of the uterus towards oestrogen stimulation. Glucocorticoids which are released during stress can turn oestrogen–dependent changes of precancerous, atypical hyperplasia formation to the more favourable development of simple and cystic hyperplasia. Glucocorticoids can also decrease the uterus's sensitivity toward oestrogen stimulation and decrease oestrogen receptor concentration.[240]

Recent evidence

One prospective cohort study was identified for inclusion.[240]

Nielsen et al. (2007)[240] included 6,760 women from the Copenhagen City Heart Study. Different self–reported stress intensities (high, moderate or light) were not associated with risk of endometrial cancer when compared to no self–reported stress (HR 0.71, 95%CI 0.42–1.21; HR 0.52, 95%CI 0.26–1.04; and, HR 0.72, 95%CI 0.28–1.89, respectively). There was also no

association when data were analysed by stress frequency. A dose–response analysis showed that for each 1–unit increase in stress level on a 7–point stress scale, there was a marginally decreased risk of endometrial cancer (HR 0.88, 95%CI 0.76–1.01). The inverse association was only significant among women receiving menopausal hormone therapy (HR 0.77, 95%CI 0.61–0.96) and women who were not overweight or obese (BMI ≤ 25 kg/m^2) (HR 0.73, 95%CI 0.86–1.24).

Appendix A Acknowledgements

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Appendix B IARC and WCRF/AICR classifications

International Agency for Research on Cancer

The International Agency for Research on Cancer (IARC) is an agency of the World Health Organization (WHO). The IARC classifies agents to which humans may be exposed, based on the strength of the scientific evidence of their potential as human cancer hazards. Each IARC monograph includes the following sections: exposure data, studies of cancer in humans, studies of cancer in experimental animals, mechanistic and other relevant data, summary, evaluation and rationale.

IARC uses standard terms to evaluate the strength of the evidence for carcinogenicity arising from human and experimental animal data. It also examines the strength of the mechanistic evidence. The evaluation categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). Importantly, risk may not be present at everyday levels of exposure. The IARC monographs identify cancer hazards even when risks are very low at current exposure levels, because new or unforeseen exposures could engender risks that are significantly higher.

IARC applies specific terms to the human and experimental animal evidence, and to the overall evaluation. See details of the methods and evaluation criteria that the IARC uses, at http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf. The various evaluation categories are summarised in Table C.1 (Appendix C).

For human epidemiologic evidence, in some instances, the categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues, such as endometrial tissue. In this report, although consideration is given to the overall carcinogenicity of an agent to humans if it has been considered in relation to endometrial cancer also, the classification as an overall carcinogen is of much less interest than the human epidemiological evidence specific to endometrial cancer.

In relation to endometrial cancer specifically, the 'List of classifications by cancer sites with sufficient or limited evidence in humans, volumes 1 to 123' indicates the following:

- Carcinogenic agents with sufficient evidence in humans:
  - Oestrogen menopausal therapy
  - Oestrogen–progestogen menopausal therapy
  - Tamoxifen
- Agents with limited evidence in humans:
  - Diethylstilboestrol

IARC monographs can be found at https://monographs.iarc.fr/

World Cancer Research Fund/American Institute for Cancer Research

The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Continuous Update Project (CUP) is a rigorous, systematic and ongoing program to present, analyse and judge the global research on how diet, nutrition and physical activity affect cancer risk and survival, and to make cancer prevention recommendations. The first and second expert reports on cancers overall were published in 1997 and 2007. Specific reports on endometrial cancer were published in 2007 and 2013, with the latter updated in 2018[xxv] as part of the Third Expert Report.

The WCRF/AICR makes recommendations based on independently conducted systematic reviews of epidemiological evidence, supported by experimental evidence from human and animal studies. It also considers plausible biological mechanisms and dose–response relationships in making judgements about causality. An expert panel judges and classifies the evidence as convincing, probable, limited or unlikely to affect cancer risk. Details of the judgement process and criteria can be found at https://www.wcrf.org/dietandcancer/judging–evidence. The grading criteria are summarised in Appendix C, Table C.2.

The main reports in relation to diet, nutrition, physical activity and risk of endometrial cancer are:

- *Diet, nutrition, physical activity and cancer: a global perspective* (World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and endometrial cancer). Available at https://www.wcrf.org/dietandcancer
- *The associations between food, nutrition and physical activity and the risk of endometrial cancer* (World Cancer Research Fund International Systematic Literature Review: the Associations between Food, Nutrition and Physical Activity and The Risk of Endometrial Cancer 2012). Available at https://www.wcrf.org/sites/default/files/endometrial–cancer–slr.pdf
- *Resources and toolkits* (World Cancer Research Fund/ American Institute for Cancer Research). Available at https://www.wcrf.org/dietandcancer/resources–and–toolkit

[xxv] Although the 2018 report was indicated to be an 'updated' report, no new evidence was reviewed beyond that contained in the 2013 report.

Appendix C IARC and WCRF/AICR categories of evidence and criteria for grading carcinogenicity

Table C.1 International Agency for Research on Cancer (2015): Categories of evidence of carcinogenicity

Overall carcinogenicity
IARC considers the body of evidence from studies in humans (across cancer sites) as well as in experimental animal studies and from mechanistic and other relevant data, to reach an overall evaluation of the carcinogenicity of the agent to humans.
Group 1—carcinogenic to humans. This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally: with less than sufficient evidence of carcinogenicity in humans but with sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans of a relevant mechanism of carcinogenicity.
Group 2A—probably carcinogenic to humans. Limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. In some cases: inadequate evidence of carcinogenicity in humans, sufficient in animals, and strong evidence of mechanism in humans. Exceptionally: limited evidence of carcinogenicity in humans provides the sole basis for classification.
Group 2B—possibly carcinogenic to humans. Limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals. In some cases: inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. In some instances: inadequate evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals and supporting evidence from mechanistic and other relevant data. In some cases there may only be strong evidence from mechanistic and other relevant data.
Group 3—not classifiable as to its carcinogenicity to humans. Inadequate evidence of carcinogenicity in humans and inadequate or limited evidence of carcinogenicity in experimental animals. Exceptionally: inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental studies and strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans. Agents that do not fall into any other group are also placed in this category.
Group 4—probably not carcinogenic to humans. Evidence suggesting lack of carcinogenicity in humans and experimental animals. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

Evidence in humans
The evidence relevant to carcinogenicity of agents from studies in humans is classified into four categories by the IARC working group.[xxvi] In some instances, the categories are used to classify the degree of evidence related to carcinogenicity in specific organs or tissues, such as breast cancer.
Sufficient evidence of carcinogenicity. The working group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is sufficient evidence is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.
Limited evidence of carcinogenicity. A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the working group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.
Inadequate evidence of carcinogenicity. The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.
Evidence suggesting lack of carcinogenicity. There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure.

Source: International Agency for Research on Cancer/World Health Organization. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Preamble. Lyon, France; 2015.

[xxvi] Note that IARC also uses the same labels (i.e. sufficient, limited, inadequate, lack of) for classifying the evidence from experimental animal studies.

Table C.2 World Cancer Research Fund/American Institute for Cancer Research (2018): Criteria for grading evidence for cancer prevention

Strong—Convincing	*Overall evidence strong enough to justify goals and recommendations to reduce cancer incidence* Causal relationship highly unlikely to be modified by new evidence in foreseeable future. Generally required: • Evidence from more than one study type and at least two independent cohort studies • No substantial unexplained heterogeneity within or between study types or in different populations regarding presence or absence of association, or direction of effect • Good quality studies to confidently exclude the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias • Presence of a plausible biological gradient ('dose–response') in the association (gradient need not be linear or in same direction across different levels of exposure, so long as this can be explained plausibly) • Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes
Strong—Probable	*Overall evidence strong enough to justify goals and recommendations to reduce cancer incidence, but not as strong as convincing category* Generally required: • Evidence from at least two independent cohort studies/at least five case–control studies • No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect • Good quality studies to confidently exclude the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias • Evidence for biological plausibility
Limited—Suggestive	*Overall evidence too limited for probable or convincing causal judgement, but suggesting direction of effect* • Evidence methodologically flawed or limited in amount, but generally showing a consistent direction of effect • Recommendations to reduce cancer incidence rarely justified Generally required: • Evidence from at least two independent cohort studies/at least five case–control studies • Direction of effect is generally consistent, although some unexplained heterogeneity may be present • Evidence for biological plausibility
Limited—No conclusion	*Evidence is so limited that no firm conclusion can be made* This category represents an entry level and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. The evidence might be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by poor quality of studies (for example, lack of adjustment for known confounders), or by any combination of these factors.

Strong—Substantial effect on risk unlikely	Evidence is strong enough to support a judgement that a particular exposure is unlikely to have a substantial causal relation to a cancer outcome. The evidence should be robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates. All of the following were generally required: • Evidence from more than one study type • Evidence from at least two independent cohort studies • Summary estimate close to 1.0 for comparison of high versus low exposure categories • No substantial unexplained heterogeneity within or between study types or in different populations • Good quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding, and selection bias • Absence of a demonstrable biological gradient ('dose–response') • Absence of strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures lead to relevant cancer outcomes

Source: World Cancer Research Fund, American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Judging the evidence. Available at www.wcrf.org/sites/default/files/judging–the–evidence.pdf.

Glossaries

Glossary 1—Epidemiological terms and study types

Absolute risk	A measure of the risk of a certain event happening, or a person's chance of developing a specific disease over a specified time period. In cancer research, it is the likelihood that a person who is free of a specific type of cancer at a given age will develop that cancer over a certain period of time.
Age–standardised incidence rate	An age–standardised rate of cancer is the rate of cancer in a given population that has been standardised to a reference population with a standard age distribution.
Attributable risk	Also known as absolute risk difference. This absolute measure of effect represents the difference between the absolute risks in two groups, usually between an exposed and unexposed group. The excess number of cases that could be explained by or could be attributed to that factor increases with the proportion of the population exposed to the factor and with the incidence rate of the disease in the population (i.e. absolute risk).
Case–control studies	Case–control studies are one of the most basic study designs for epidemiological research. In case–control studies, people with the outcome or disease (cases) and an appropriate group of controls without the outcome or disease (controls) are selected and the information obtained about their previous exposure/non–exposure to the factor under study, such as reproductive history or diet. It is a retrospective design.
Cochrane review	Cochrane Reviews are systematic summaries of evidence of the effects of healthcare interventions. Cochrane reviews are prepared using Review Manager (RevMan) software provided by the Collaboration, and adhere to a structured format that is described in the Cochrane Handbook for Systematic Reviews of Interventions.
Cohort studies	Cohort designs are widely used in epidemiological research. Participants do not have the disease of interest, such as endometrial cancer, at the start of the study, but are followed prospectively through time. The occurrence or incidence of the disease is compared between groups of people exposed to the factor under study and groups of people not exposed.
Confidence intervals	A range of values that has a specified probability of containing the true point estimate of effect. The most common specified probability is 95%, akin to p=0.05. The narrower the interval the more precise the estimate of the risk and the less likely that the risk would be subject to chance variation. A relative risk is generally considered statistically significant when the value of 1.0 is not in the 95% confidence interval.

Confounding	Confounding occurs when an exposure and an outcome are associated with each other simply because both are acted on by a third variable (confounder), not because the exposure has a causal effect on the outcome.
Cumulative risk	A measure of the total risk that a certain event will happen during a given period of time.
Hazard ratio	A measure of how often a particular event happens in one group compared to how often it happens in another group, over time.
Heterogeneity	Differences between studies that impact on the interpretation of the results and the ability to draw any legitimate or meaningful conclusions. Heterogeneity can be quantified using the I^2 statistic, which describes the percentage of total variation across studies in a meta–analysis that is due to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% can be considered as low, moderate, and high. Other measures of heterogeneity include Tau which is a measure of the dispersion of true effect sizes between studies when fitting a random–effects model in terms of the scale of the effect size, i.e. it is in the same 'units' as the results measure.
Meta–analysis (following systematic review)	In a meta–analysis similar studies that address the same research question are identified through systematic review and the results are statistically combined and analysed, and the overall result interpreted as if derived from one large study. This method gives greater statistical power to detect important associations. It allows the detection of less obvious associations as well as the examination of dose–response relationships often not possible in individual studies.
Nested case–control studies	Nested case–control studies are carried out within an existing cohort study. All the cases in the cohort are compared with a matched sample of the participants who have not developed cancer by the time of disease occurrence in the cases (controls). It has many of the strengths of the cohort study including minimising selection bias compared with a case–control study and having exposure information collected at inception and/or during the course of follow–up.
Odds ratio (OR)	Uses the odds of developing a disease in both groups to calculate a relative measure between two groups rather than the risk. As a rule, retrospective study designs will only report odds ratios (ORs), whereas prospective study designs, like the cohort study, will generally report a relative risk (RR) estimate.
Point estimation (size of effect)	Refers to the measure of effect or point estimate provided in the results of each study (e.g. mean difference, relative risk, odds ratio, hazard ratio, sensitivity, specificity). In the case of a meta–analysis it is the summary or pooled measure of effect from the studies included in the systematic review (e.g. weighted mean difference, summary or pooled relative risk). These point estimates are calculated in comparison to either doing nothing or versus an active control.

Pooled analysis	Pooled analyses are a type of meta–analysis but in pooled analyses individual–level data from various published or unpublished epidemiological studies of a similar type – usually prospective cohort studies – are combined and re–analysed as a 'single study'. This creates a larger data set and increased statistical power.
Population–attributable risk	Population attributable fraction (PAF) is the proportional reduction in population disease or mortality that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario (eg. no tobacco use).
Prospective cohort studies	A type of cohort study that follows a group of similar people (a cohort) and studies them over time to determine how certain factors affect rates of a certain outcome. They are often referred to as the gold standard of observational epidemiological designs as they are less prone to bias, recall error and have higher validity than other observational study designs.
Randomised controlled trials	Randomised controlled trials (RCTs) are well–controlled, experimental studies in humans. In RCTs the unit of experimentation (e.g. people, or a cluster of people) is allocated to either an intervention (the factor under study) group or a control group, using a random mechanism (such as a coin toss, random number table, computer–generated random numbers) and the outcomes from each group are compared. RCTs are considered the gold standard in clinical trials as they are the most rigorous and reliable.
Relative risk (RR)	Relative risk (RR) is the most common metric of comparative risk reported throughout this report, and it compares the absolute risk of a group of people who are exposed to a risk factor with the absolute risk of a group of people who are not exposed to the risk factor. It is sometimes referred to as the 'risk ratio'. Depending on the study design and statistical method used, the relative risk can be presented using different measures of effect, such as the incidence rate ratio (also called the standardised incidence ratio) and hazard ratio.
Retrospective cohort studies	A type of cohort study whereby cohorts (groups of people exposed and no exposed) are defined at a point of time in the past and information collected on subsequent outcomes. All of the events – exposure to the risk factor, latent period, and subsequent development of the disease – have already occurred in the past. Data are simply collected in the present.
Standardised incidence ratio	Standardised incidence ratio is the disease incidence in a cohort compared to in the general population, i.e. the ratio of the observed number of cases compared to the expected number of cases. The expected number of cases is computed using age–specific rates from a reference population, weighted according to the age structure of the study population.

Glossary 2—Endometrial cancer and exposures terms

Acrylamide	Water soluble white solid used in industries such as papermaking, building constructions and water treatment.
Cowden syndrome	Autosomal dominant inherited disorder characterised by multiple benign hamartomas, typically on the skin, mucous membranes, and the intestine, and a susceptibility to several other cancers.
Endometrial cancer	Cancer that begins in the lining of the uterus (endometrium). They are linked to excess oestrogen in the body. They are generally slow growing and less likely to spread.
Endometrial cancer – type I	Type I endometrial cancer is also known as endometrioid carcinoma. Type I endometrial cancer is the most common type of endometrial cancer and uterine malignancy overall. Type I endometrial tumours are mostly adenocarcinomas that begin in the glandular cells of the endometrium. Type I endometrial cancers are generally well– to moderately well–differentiated and are considered low–grade. This type of endometrial cancer has a favourable prognosis and typically presents at an early stage with abnormal uterine bleeding.
Endometrial cancer – type II	Type II endomterials are much less common (about 10% of endometrial cancers are Type II lesions). In contrast to type I tumours, type II tumours are not oestrogen driven and are either poorly differentiated endometrioid (grade 3) or non–endometrioid lesions such as serous carcinoma, clear cell carcinoma and mucinous carcinoma. These tumours are often high–grade, have a poor prognosis, and a tendency to deeply invade the myometrium and metastasise.
Endometrial hyperplasia	Characterised by abnormal proliferation of endometrial glands resulting in a greater gland to stroma ratio compared with normal proliferative endometrium.
Endometrial Intraepithelial Neoplasia (EIN)	A precancerous condition in which areas of the lining of the uterus grow too thick.
Endometrial polyps	Small, soft growths attached to the inner wall of the uterus. Polyps are usually benign (non–cancerous), although some may eventually turn into cancer.
Endometriosis	Condition in which the endometrium grows outside of the uterus and causes pain and infertility.
Glycaemic load (GL)	Number that estimates how much the food will raise a person's blood glucose level after consumption. One unit of GL is approximately equivalent to the effect of consuming one gram of glucose. Glycaemic load is based on the glycaemic index (GI) and is calculated by multiplying the grams of available carbohydrate in the food with the food's GI and then dividing by 100.
Lynch syndrome	Lynch syndrome is an autosomal dominant inherited condition due mismatch repair genes mutation that increases a person's risk of developing certain types of cancer. Lynch syndrome, previously known as hereditary non–polyposis colorectal cancer, is caused by a mutation in one of several DNA mismatch repair genes including *MLH1*, *MSH2*, *MSH6*, and *PMS2*.

Microsatellite instability (MSI)	A change that occurs in the DNA of certain cells (such as tumour cells) in which the number of repeats of microsatellites (short, repeated sequences of DNA) is different than the number of repeats that was in the DNA when it was inherited. The cause of microsatellite instability may be a defect in the ability to repair mistakes made when DNA is copied in the cell.
Mismatch repair (MMR) gene mutations	Describes cells that have mutations (changes) in certain genes that are involved in correcting mistakes made when DNA is copied in a cell. Mismatch repair (MMR) deficient cells usually have many DNA mutations, which may lead to cancer.
Myometrium	Smooth muscle tissue that makes up most of the uterus.
Oestrogen	The primary female sex hormone. It is made mainly by the ovaries and helps regulate the female reproductive cycle.
Polycystic ovary syndrome (PCOS)	A hormonal disorder that causes the ovaries to produce too many male hormones, which affects the development and release of the eggs.
Progesterone	Naturally–occurring progestogen; predominantly produced by the ovaries in cycling premenopausal women and in low doses by the adrenal glands in women of all ages.
Progestins	Synthetic progestogens including compounds such as medtrocyprogesterone acetate (MPA), levonorgestrel, and norethindrone acetate (NETA).
Progestogen	Any substance, natural or artificial (that is, synthetic), that exerts progesterone–like activity via the activation of progesterone receptors.
Uterine cancer	Cancer that forms in tissues of the uterus (the small, hollow, pear–shaped organ in a woman's pelvis in which a foetus develops). Two types of uterine cancer are endometrial cancer (cancer that begins in cells lining the uterus) and uterine sarcoma (a rare cancer that begins in muscle or other tissues in the uterus).
Uterine sarcoma	A cancer affecting the muscle tissue (myometrium) or the connective tissue (stroma) of the uterus.

Abbreviations

AH	atypical hyperplasia
AICR	American Institute for Cancer Research
AIHW	Australian Institute of Health and Welfare
ANECS	Australian National Endometrial Cancer Study
AR	absolute risk
BMI	body mass index
BRCA1/2	BReast CAncer 1/2 gene mutation
CI	confidence interval
combined MHT	combined oestrogen–progestogen menopausal hormone therapy
CORE trial	Continuing Outcomes Relevant to Evista trial
COX	cyclooxygenase
CUP Endometrial SLR	Continuous Update Project Systematic Literature Review
DNA	deoxyribonucleic acid
E2C2	Epidemiology of Endometrial Cancer Consortium
E3N	Etude Epidémiologique auprès des femmes de la mutuelle générale de l'éducation nationale
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
E–cadherin	epithelial cadherin
EIN	endometrial intraepithelial neoplasia
EPCAM	epithelial cellular adhesion molecule
EPIC	European Prospective Investigation into Cancer and Nutrition
EPIC–Italy	European Prospective Investigation into Cancer and Nutrition (cohort in Italy: Florence, Milan, Ragusa province, Turin and Naples)
ETS	environmental tobacco smoke
FDR	First–degree relative
g/d	grams per day
GI	glycaemic index
GL	glycaemic load
GnRH	gonadotropin–releasing hormone
GP	general practitioner
HER2	human epidermal growth factor receptor 2

HMG–CoA	3–hydroxy–3–methylglutaryl–coenzyme
HR	hazard ratio (also used for hormone receptor in places)
HRT	hormone replacement therapy
IARC	International Agency for Research on Cancer
IBIS	International Breast Intervention Study
ICD–10	International Classification of Diseases, Tenth Edition
IGF1	insulin–like growth factor 1
IPD	individual patient data
IRR	incident rate ratio
IUD	intrauterine device
IVF	in vitro fertilisation
kg/m^2	kilograms per square metre
KRAS gene	Ki–ras2 Kirsten rat sarcoma viral oncogene homolog
m	metre
MET	metabolic equivalent
mg	milligrams
MHT	menopausal hormone therapy
MMR	mismatch repair
MMRd	mismatch repair deficiency
MORE study	Multiple Outcomes of Raloxifene Evaluation study
MSH2	MutS Homolog 2
MSI	Microsatellite instability
µg/d	micrograms per day
NCI	National Cancer Institute
NHMRC	National Health and Medical Research Council
NIH–AARP	National Institutes of Health–American Association of Retired Persons (Diet and Health Study)
NOWAC	Norwegian Women and Cancer Study
NSABP	National Surgical Adjuvant Breast Project
NSAID	non–steroidal anti–inflammatory drugs
NSW	New South Wales
OR	odds ratio
PCOS	polycystic ovarian syndrome
PHTS	PTEN Hamartoma Tumour Syndrome

PTEN	phosphatase and tensin homolog
RCT	randomised controlled trial
RR	relative risk, or risk estimate
SEER	Surveillance, Epidemiology and End Results program
SHBG	sex hormone binding globulin
SIR	standardised incidence ratio
SDR	second degree relative
SERMs	Selective oestrogen receptor modulators
SLR	systematic literature review
STAR	study of Tamoxifen and Raloxifene
TCGA	The Cancer Genome Atlas
TNF	tumour necrosis factor
TP53	tumour protein 53
UK	United Kingdom
US	United States
WC	waist circumference
WCRF	World Cancer Research Fund
WHI	Women's Health Initiative
WHO	World Health Organization

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