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# Etiology of gynecological cancers: update and future perspectives

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# Etiology of gynecological cancers: update and future perspectives

## SUMMARY

Globally, gynecological cancers comprise three of the seven most common female cancers and are responsible for more than 1,000,000 new cases and 500,000 deaths annually. This review summarizes current knowledge regarding the role of non-genetic factors in gynecological cancer etiology and survival, focusing on those that are potentially amenable to intervention. Strong associations with use of exogenous hormones are countered by opposing risks of breast cancer, thus current hormonal preparations are not an option for prevention. Weight control would reduce risk of endometrial cancer but this and other lifestyle modifications are unlikely to have a major effect on gynecological cancer mortality rates. There is little information regarding the potential for lifestyle changes to improve outcomes for women with gynecological cancer.

## FUTURE PERSPECTIVE

It is now well recognized that the etiology of gynecological cancer can differ for different histological subtypes, furthermore pathological classification of ovarian cancers is evolving [1] and molecular studies are revealing different molecular subtypes within a single histological group [2]. Future studies must take this heterogeneity into account. Pooling of data across multiple studies within large international consortia as well as the increased numbers of cases available from prospective studies as these mature will greatly enhance our ability to evaluate risk factors by subtype,thereby clarifying the patterns and magnitude of risk (or benefit) associated with less well understood and less common exposures. . Together with the explosion in the amount of genetic information available for study participants, this

will also allow more robust evaluations of interactions between genetic and non-genetic risk factors and more reliable risk prediction . There is also increasing interest in the potential for changes in lifestyle to improve both quality of life and prognosis after a diagnosis of cancer with more studies and trials evaluating the role of behaviors such as physical activity and diet, as well as common medications such as those used for diabetic control, among cancer survivors. This will allow us to provide women with better evidence-based guidance as to how they can minimize their cancer risks and/or improve outcomes after a cancer diagnosis.

## EXECUTIVE SUMMARY

### Background

- Worldwide, gynecological cancers comprise three of the top seven cancers in women with more than 1 million new cases and half a million deaths every year.

### Review of epidemiological evidence

- Tubal sterilization reduces a woman's risk of developing ovarian cancer.
- Increasing parity and oral contraceptive use dramatically reduce risk of ovarian and endometrial cancer, but slightly increase risk of cervical cancer.
- Estrogen-only hormone replacement therapy (HRT) increases risk of ovarian and endometrial cancer; addition of progesterone on most or all days appears to mitigate this increase and may even reduce risk of endometrial cancer .
- There is currently little evidence that fertility drugs increase cancer risk, but larger studies are required before we can confidently say there is no association.
- Obesity greatly increases a woman's risk of endometrial and, to a lesser extent, ovarian cancer.

- Physical activity, a diet with a low glycemic index and coffee intake reduce risk of endometrial cancer, but there is little evidence for a relation between diet and other gynecological cancers.
- Smoking increases a woman's risk of developing cervical cancer and the mucinous subtype of ovarian cancer.

**Opportunities for prevention**

- Current hormonal formulations do not provide a practical way to reduce risk of gynecological cancer risk because of adverse effects at other cancer sites, however localized delivery of hormones may overcome some of these problems.
- Maintenance of a healthy body weight will greatly reduce a woman's risk of endometrial cancer and following standard health guidelines regarding physical activity, diet and smoking may confer modest benefits on risk of both endometrial and ovarian cancer.

**Survival after a diagnosis of gynecological cancer**

- There is little information regarding the role of lifestyle in gynecological cancer survival.

**Conclusion**

- With the exception of weight reduction to reduce risk of endometrial cancer, current options for prevention are limited.
- Further evidence is required before we can reliably inform women regarding potential lifestyle choices to improve cancer survival.

Worldwide, more than one million women are diagnosed with cancers of the female genital tract, including the ovaries, fallopian tubes, uterus, cervix, vulva and vagina, every year and almost half a million women die from their disease [101]. Cancers of the cervix, ovary and uterus all rank among the top seven most common cancers in women (Figure 1), although there is considerable geographic variation in their relative frequency. Globally, cervical cancer is the second most common cancer in women and the most common of the gynecological cancers, affecting 530,000 women every year; however it is now primarily a disease of less developed countries which account for 87% of all new cases [101]. In more developed countries, effective screening programs have led to reductions in the incidence of invasive cervical cancer such that it now ranks only 11$^{th}$ in terms of the number of new cases each year. In contrast, uterine and ovarian cancer are less common at the global level, ranking sixth and seventh in women with 320,000 and 229,000 new cases per year, respectively, but they are relatively more important causes of morbidity and mortality in higher-income countries. The incidence of cancers at the other gynecological sites including the vulva and vagina is low in all areas of the world [102].

Gynecological cancers are heterogeneous diseases and there is increasing evidence that histologically distinct subtypes arise via different etiological pathways. The following discussion of ovarian and uterine cancer will relate to epithelial cancers of the ovary and endometrium, the lining of the uterus, as these comprise the majority of all ovarian and uterine cancers, respectively, and have been the focus of most research. Within the group of epithelial cancers, ovarian tumors can be either frankly invasive or borderline (low malignant potential) in nature and they fall into four major subtypes. The most common and most aggressive invasive ovarian cancers are high-grade serous cancers with cells that resemble the lining of the fallopian tube [3]. [Note: although high-grade serous ovarian cancers are now

thought to originate in the fallopian tube and not the ovary, these cancers will, by convention, be considered as ovarian for the purpose of this review.] Less common are endometrioid cancers that resemble endometrial cells, mucinous cancers that resemble cells of the endocervical or, more commonly, intestinal epithelium, or clear cell cancers [3]; borderline ovarian cancers are usually serous or mucinous tumors. In contrast, the majority of invasive endometrial cancers are low-grade, early stage endometrioid tumors that arise on a background of endometrial hyperplasia. These are often described as Type 1 or estrogen-dependent cancers, in contrast to the less common but more aggressive serous and clear cell cancers that are often described as Type 2 or non-estrogen-dependent. The majority of cervical cancers are squamous cell cancers or adenocarcinomas.

The following sections will review the current status of knowledge regarding the role of non-genetic factors in the etiology of, and survival from the most common gynecological cancers, focusing on those that are potentially modifiable and therefore present opportunities to reduce morbidity and mortality. It is important, however, to note that both ovarian and endometrial cancer have a strong genetic component. Mutations in the *BRCA1* and *BRCA2* genes not only predispose a woman to developing breast cancer but carriers also have a 10-60% lifetime risk of developing ovarian cancer compared to about 1% in the general population [4]. Mutations in the mismatch repair genes *MLH1*, *MSH2*, *MSH6* and *PMS2*, collectively known as Lynch syndrome, not only predispose a woman to developing colorectal cancer but carriers also have a 16-50% risk of developing endometrial cancer before age 70 years [5] as well as a modestly increased risk of ovarian cancer [4]. It is well established that the primary cause of cervical cancer is infection with a carcinogenic strain of the human papillomavirus (HPV) and HPV infection is also thought to play a role in the development of vulva and vaginal cancers [6]. Although other factors such as smoking and

oral contraceptive use almost certainly modify risk among those carrying a high-risk HPV infection, the following discussion will focus mainly on the non-HPV-related gynecological cancers, specifically epithelial ovarian cancer (including the closely related fallopian tube and primary peritoneal cancers) and endometrial cancer.

## REVIEW OF EPIDEMIOLOGICAL EVIDENCE

### Medical history

If a woman has her uterus and/or ovaries completely removed she is clearly no longer at risk of developing cancer at those sites however, as it now appears many high grade serous cancers actually arise in the fallopian tubes, salpingectomy should also be performed to reduce risk of so-called 'ovarian' cancer. Although a radical intervention, surgery may be appropriate for women who carry a high-risk genetic mutation. It is, however, important to note that a woman who has had her ovaries removed can still develop a cancer that is histologically and clinically identical to ovarian cancer on the peritoneal surface. Early studies suggested that hysterectomy without oophorectomy could also protect a woman against developing ovarian cancer, however more recent studies have not reported the same inverse associations [7], possibly because of changing patterns of hysterectomy. This raises questions about the utility of hysterectomy as a potential strategy to reduce risk of ovarian cancer. In contrast, there are more consistent data suggesting that tubal sterilization does reduce a woman's subsequent risk of ovarian cancer [8], possibly because it blocks retrograde flow of potentially carcinogenic factors such as talcum powder (see below) to the ovaries, or because it leads to changes in the hormonal environment.

Studies have consistently shown that women with a history of endometriosis have a two- to three-fold increased risk of developing clear cell and endometrioid cancers of the ovary [9]. A recent pooled analysis suggested they were also at increased risk of developing

low-grade serous cancers but risks were not elevated for high-grade serous, mucinous or borderline cancers [9]. The data regarding endometrial cancer are less clear although, on balance, it appears that a history of endometriosis does not increase a woman's risk of endometrial cancer [10]. In contrast, women with diabetes [11] or polycystic ovary syndrome [12] have an approximately two-fold increased risk of developing endometrial cancer, even after adjusting for body-mass index which is associated with both of these conditions as well as being a strong risk factor for endometrial cancer (see below). A history of fibroids also increases a woman's risk of going on to develop endometrial cancer, possibly because both conditions are associated with increased estrogen exposure [10].

**Reproductive history**

It is well known that reproductive history plays a major role in determining a woman's risk of developing both endometrial and ovarian cancer. Risk of endometrial cancer is associated with the length of a woman's reproductive life such that it is reduced by 6-9% for every year that menarche is delayed or menopause advanced [13]. Risk of ovarian cancer also appears to be lower among women who undergo menopause at a younger age [14], however evidence for an association with age at menarche is less clear. Risk is also greatly reduced among parous women and decreases with increasing parity such that women who have had three or more children have about half the risk of developing either of these cancers compared to women who have not had children [15,16]. Furthermore, the protective effects of pregnancy appear to persist for several decades, although the greatest reductions in risk are seen for women who were older at the time of their last pregnancy [17,18] and/or for more recent pregnancies. While some studies have also suggested that multiple pregnancies, the sex of the baby and the spacing between pregnancies may influence cancer risk by altering the hormonal environment [7,19,20], there are currently no convincing data to support this.

In marked contrast to the strong inverse associations seen for ovarian and endometrial cancer, pregnancy appears to increase a woman's risk of developing cervical cancer even after adjusting for markers of sexual behavior and HPV infection. In an international analysis that pooled data from more than 10,000 women with invasive cervical cancer and 30,000 controls, each additional full-term pregnancy was associated with an approximately 10% increase in risk [21] that was seen in both the whole study population and among the subset of women who carried a high-risk HPV infection. The association was somewhat stronger for squamous cell cancers than for adenocarcinomas [22].

**Exogenous hormones**

It is also well established that use of the oral contraceptive pill (OCP) reduces a woman's risk of both endometrial and ovarian cancer [15,23]. Risk decreases with increasing duration of OCP use, such that the risk among women who have used the OCP for more than 10 years is less than 60% of that of women who have not used the OCP and although, as for pregnancy, the protective effect is reduced over time, it remains significant for several decades after stopping [23,24]. There is some suggestion, however, that the association between OCP use and ovarian cancer may differ for the various histological subtypes, with strong inverse associations seen for invasive serous, clear cell and endometrioid cancers but little or no reduction in risk for mucinous or borderline cancers [23]. Again, as for pregnancy, the relation is reversed for cervical cancer with current OCP users experiencing an almost two-fold increased risk of cervical cancer after 5 years of use, although risk returns to that of never-users by about 10 years after last use [25]. The association is similar for both squamous cell and adenocarcinomas [22] and is also seen among women who carry a high-risk HPV infection [25].

It has long been recognized that estrogen causes endometrial hyperplasia, a precursor to Type 1 endometrial cancer, and that this effect is mitigated by progesterone. As a result, exposure of the uterus to estrogen in the absence of progesterone is a very strong risk factor for endometrial cancer [26] and current guidelines recommend that a woman with an intact uterus should not be prescribed estrogen-only hormone replacement therapy (HRT)[27]. Current or recent use of HRT also increases a woman's risk of developing ovarian cancer by approximately 50%, with stronger associations reported for estrogen alone than for combined estrogen-progesterone preparations [28,29]. In contrast, use of combined HRT does not appear to increase risk of endometrial cancer with recent observational studies reporting little or no association with use of sequential preparations with at least 10 days of progesterone per month and reduced risks among women who have used continuous combined preparations [26,30]. Furthermore, although few participants in the Women' Health Initiative HRT trial developed gynecological cancers, this also suggested a non-significant decrease in risk of endometrial cancer among women randomized to receive combined HRT, although non-significant increases were seen for invasive ovarian and cervical cancer [31]. This pattern of risk is in marked contrast to that seen for breast cancer where it is the combined preparations that significantly increase risk, with possible reductions in risk seen among women who have had a hysterectomy and use estrogen-only HRT [32].

Despite the well recognized benefits of OCP use on risk of endometrial and ovarian cancer, the increased risks of cervical (and breast) cancer seen among current and recent users mean this is not a viable way to prevent cancer at the population level. There has thus been considerable interest in the potential benefits of locally administered progesterone for reducing risk of, or even treating early endometrial cancers, particularly among young women who wish to preserve their fertility or among women who are unfit for surgery.

Levonorgestrel-impregnated intrauterine devices (LNG-IUD) were introduced in the early 1990s and are approved for contraception, treatment of menorrhagia and to prevent endometrial hyperplasia in women using estrogen replacement therapy. There is increasing evidence that they can also reverse endometrial hyperplasia and they have been used with mixed results among women with early endometrial cancer [33]. Unlike oral and injected contraceptives, the hormone is delivered directly to the uterus, however an appreciable amount does make its way into the circulation [34] so systemic effects are possible. Given the relatively recent introduction of these devices and thus low usage among the older women who are at greatest risk of developing cancer, current studies do not yet have sufficient power to assess the relation between LNG-IUD use and incidence of cancer at different sites. With the increasing use of these devices it is important to understand the likely population impact of LNG-IUD use and particularly the potential benefits for sites such as the endometrium and ovary in comparison to the potential harms in relation to cancer of the breast and cervix.

**Breastfeeding**

A common feature of both pregnancy and OCP use is that they suppress ovulation and the physical and hormonal consequences of this may explain the reduced risk of ovarian and endometrial cancer among women who have had children and/or used the OCP. The same is true of breastfeeding, at least for the first 6-12 months following birth [35], and a number of case-control studies have shown that, among parous women, those who have breastfed for longer have a reduced risk of ovarian cancer (reviewed in [36]). On this basis the 2007 World Cancer Research Fund (WCRF) and American Institute of Cancer Research (AICR) report on Food, Nutrition, Physical Activity, and the Prevention of Cancer concluded that there was limited evidence to suggest that breastfeeding reduces a woman's risk of developing ovarian cancer by approximately 4% for every 6 months of breastfeeding [36]. A more recent meta-

analysis reported a similar risk reduction of 5% per 5 months breastfeeding based on cohort data [37] but the 2014 update to the WCRF/AICR report again concluded the evidence for protection was limited [38]. However, despite the very similar associations seen for ovarian and endometrial cancer with respect to parity and OCP use, the few studies that have assessed the relation between breastfeeding and endometrial cancer risk have reported little or no association. As a result the 2013 update of the WCRF/AICR report on endometrial cancer found there was insufficient evidence to draw any conclusions regarding the relation with breastfeeding [39].

**Infertility treatment**

In contrast to the reproductive exposures discussed above that suppress ovulation, many infertility treatments are designed to stimulate hyperovulation and this has led to concerns that they might increase a woman's risk of developing cancer. Initial concerns came from two small studies suggesting that women who had taken fertility drugs did indeed have an increased risk of ovarian cancer [16,40]. Subsequent studies have generally not shown significant associations between use of fertility drugs and risk of ovarian [41], endometrial [42,43] or cervical cancer [44] overall, but some have reported significant or non-significant increased risks for specific fertility drugs [42,43], women who have undergone a greater number of cycles of treatment [42,43] or with increasing duration of follow-up [43]. Most studies have, however, had limited power to detect an association, particularly in sub-group analyses. This is largely due to the small numbers of cancer cases among fertility drug users because the majority have not yet reached the age when gynecological cancer becomes common. Other limitations include relatively short periods of follow-up and an inability to control for potentially important confounding factors such as parity and oral contraceptive use. It is also important to note that the majority of women in the current studies were treated

with fertility drugs more than a decade ago and the drugs and doses used have changed since then. As a result, there is currently no convincing evidence that use of fertility drugs does significantly increase a woman's risk of developing cancer, but we cannot yet say with any confidence that there is no increase in risk.

**Body size**

In most high-income countries the prevalence of overweight and obesity has increased dramatically in recent decades [45]. After menopause, fat cells are the primary source of endogenous estrogen and, among post-menopausal women who do not take HRT, obesity is strongly related to estrogen levels [46] and thus a potential risk factor for hormonal cancers. Other potentially carcinogenic consequences of obesity include its effects on glucose metabolism and the wide range of adipocytokines and inflammatory mediators that are produced by adipose tissue and altered in concentration among obese individuals [47].

It is well known that obesity is a major risk factor for endometrial cancer with risk increasing by approximately 50% for every 5-unit increase in BMI [39] and with stronger associations seen among women who have never used HRT [48]. Recent studies suggest that, although most strongly associated with the more common low-grade Type 1 cancers, obesity also increases risk of the more aggressive non-endometrioid Type 2 cancers, albeit to a lesser extent [49,50]. Further work has suggested that the strongest associations are with adult weight gain and recent weight [51] and, encouragingly, there is some evidence that previously obese women are no longer at elevated risk if they lose weight and return to a normal BMI [51,52].

Individual studies evaluating the relation between body-size and risk of ovarian cancer have given inconsistent results, however two recent pooled analyses reported significant associations between increasing body size and risk of developing ovarian cancer [53,54]. In both cases, subtype-specific analyses suggested that the association was stronger

for borderline serous cancers (24-29% increase per 5 BMI units), endometrioid (8-17%) and mucinous cancers (12-19%), with no increase in risk of invasive serous cancers, although in the first analysis the differences between the subtypes were not statistically significant. In the first study, the association was only seen among women who had never taken HRT [53], however this difference was not seen in the second study which considered pre- and post-menopausal women and the different histological subtypes separately [54]. Together, these studies suggest that ovarian cancer should be added to the list of obesity-related cancers, but raise the possibility that obesity only increases risk of some histological subtypes of ovarian cancer, and not the more aggressive high-grade serous cancers that account for the majority of deaths. There is little evidence that obesity affects risk of invasive cervical cancer [22].

**Physical activity**

Given the strong associations between obesity and risk of endometrial cancer it is plausible that physical activity might reduce risk, however separating effects of physical activity from those of obesity can be a challenge. A number of cohort studies have now reported that increased physical activity is associated with a lower risk of endometrial cancer that is independent of any effect of obesity and, on this basis, the 2013 WCRF/AICR report found that there was now sufficient evidence to conclude that physical activity probably does reduce risk of endometrial cancer [39]. The data for ovarian cancer are, however, less clear. While a 2007 meta-analysis found that increasing physical activity was associated with a reduced risk of ovarian cancer, this was based primarily on data from case-control studies and the few cohort studies that have investigated this relationship have generally not reported any association [55].

**Diet**

Although many studies have investigated the relationship between diet and risk of gynecological cancer, the results have been very inconsistent. In the 2013 WCRF/AICR endometrial cancer update, the review team concluded that there was sufficient evidence only to suggest a probable causal relationship with increasing glycemic load [39]. Notably the suggestive inverse association with non-starchy vegetables and positive association with red meat reported in the 2007 report [36] were not confirmed in the 2013 update which considered only data from cohort studies. As for endometrial cancer, the previously noted suggestive inverse association with non-starchy vegetables [36] was not confirmed in the WCRF/AICR 2014 ovarian cancer update [38] which did not find any evidence for an association between diet and ovarian cancer risk. [56] There is also little convincing evidence for a role of diet in the etiology of cervical cancer [36].

**Tea & coffee**

There has been considerable interest in the relation between coffee and tea drinking and cancer risk because tea, in particular, is a rich source of antioxidant polyphenols.
The 2013 WCRF/AICR report concluded there was now sufficient evidence to suggest a probable inverse relation between coffee consumption and risk of endometrial cancer, but that there was insufficient evidence to draw any conclusions regarding tea drinking [39].
There is currently no evidence for an association between coffee consumption and risk of ovarian cancer [57]. Data regarding the overall relation between tea consumption and risk are inconsistent [57,58], but green tea has been associated with reduced risks of both ovarian and endometrial cancer [58,59] although further data from prospective studies are required before concluding that this association is real.

**Smoking & alcohol consumption**

Current and, to a lesser extent, past smokers are at increased risk of developing squamous cell cancers but not adenocarcinomas of the cervix, with similar associations seen overall and among women who carry a high-risk HPV infection [22,60]. It is now also fairly clear that smoking increases the risk of the relatively uncommon mucinous subtype of ovarian cancer with pooled analyses showing 30-80% increases in risk of mucinous cancers, particularly borderline mucinous cancers, among current smokers [61,62]. In contrast, the same analyses suggested that smokers were at lower risk of developing endometrioid or clear cell ovarian cancers, a pattern that is consistent with the previously reported inverse association between smoking and risk of endometrial cancer [63]. This somewhat surprising observation has been attributed to the fact that smokers tend to have lower circulating estrogen levels and earlier menopause than non-smokers [64].

While increasing consumption of alcohol is now well known to increase risk of breast cancer [36], there is currently little evidence to suggest that it increases risk of either endometrial [65] or ovarian cancer [66], with some studies even suggesting inverse associations with wine intake [66].

**Non-steroidal anti-inflammatory drugs**

Cancer is inherently an inflammatory process and there has been considerable interest in the potential for non-steroidal anti-inflammatory drugs (NSAIDs) to reduce cancer risk. Individual studies of gynecological cancer have not reported consistent associations however a meta-analysis of the 4 cohort and 5 case-control studies published prior to 2011 suggested that use of aspirin was associated with a reduction in risk of endometrial cancer, particularly among obese women [67]. Since this report, another case-control study has reported an inverse association with aspirin but not non-aspirin NSAIDs [68], but a cohort study found no

compelling evidence for an association [69]. The data for ovarian cancer also suggest a possible inverse association between use of NSAIDs and risk of invasive ovarian cancer although the results of case-control and cohort studies are not consistent. A large pooled analysis of case-control data reported a significant inverse association between use of aspirin and risk of ovarian cancer and a similar, but non-significant, association for non-aspirin NSAIDs [70]. In contrast, a meta-analysis of six cohort studies found a borderline significant association for non-aspirin NSAIDs but no association with aspirin, although a non-significant inverse association was again seen for case-control studies [71]. A recent study of cervical cancer found no association with use of aspirin or non-aspirin NSAIDs [72]. Further prospective data are required before any clear conclusions can be drawn regarding the potential for aspirin to reduce risk of gynecological cancers.

**Talcum powder**

Case-control studies have consistently shown modestly increased risks of ovarian cancer among women who use talcum powder in the perineal region, with no such association observed for use of talc on other body sites [73]. Confidence that this is a true causal effect is however weakened by the fact that more frequent talc users do not appear to be at any greater risk than occasional users [73]. Although one early study suggested that use of talcum powder was also associated with increased risk of endometrial cancer, subsequent studies have not confirmed this [74,75] although in one, more than 20 years of talcum powder use on a diaphragm was associated with a significant 3-fold increased risk [74]. This estimate was, however, based on only 23 exposed cases and requires confirmation before any conclusions can be drawn. It is important to note that current studies include mostly older women in whom the reported prevalence of genital talc use ranges up to 45% [73]. Anecdotally, talc use

is now much less common among younger women thus any potential cancer risks associated with use may become less important over time.

## OPPORTUNITIES FOR PREVENTION

Cervical cancer does not develop in the absence of HPV infection thus the most effective way to prevent cervical cancer would be to eliminate infection. The introduction of vaccination against the most common high-risk HPV types in many developed countries should go some way towards achieving this. As discussed above, factors that appear to further increase risk among women who are HPV-positive include pregnancy, OCP use and smoking. Although it has been estimated that almost 10% of all cervical cancers in the UK, predominantly those among younger women who are more likely to be current or recent OCP users, could be attributed to their OCP use [76], neither pregnancy nor OCP use provide a practical target for intervention. In particular, the number of cases of cervical and breast cancer that could potentially be prevented if women did not use the OCP would be greatly outweighed by the additional cases of ovarian and endometrial cancer that would result [76]. The only potentially modifiable exposure is therefore tobacco smoking and it has been estimated that if women did not smoke approximately 7% of cervical cancers could be prevented in the UK [77].

As noted above and summarized in Table 1, the factors that have the greatest influence on risk of ovarian and endometrial cancer are those relating to reproductive behavior and hormones, with greatly reduced risks of both cancers seen among women who have had children and or used the OCP. It has been estimated that OCP use prevents approximately 9% of ovarian cancers and 17% of endometrial cancers that would otherwise occur in the UK [76], and that worldwide over the next few decades, up to 30,000 new ovarian cancers alone will be prevented each year because women use the OCP [23]. In contrast, the mixed patterns of risk seen with use of different types of HRT and the fact that estrogen-only

HRT is rarely prescribed to women with an intact uterus who are at risk of endometrial cancer, mean that HRT has much less of an impact and only about 1% of ovarian and endometrial cancers can be attributed to use of postmenopausal hormones [76]. Overall, however, the relations between use of exogenous hormones and cancer are complex with opposing patterns of risk seen for different combinations of estrogen and progesterone and for cancers at different body sites. Although the development of IUDs that administer progesterone locally within the uterus may mitigate the increased risks of cancer at non-gynecological sites, further data are required to assess the overall risks and benefits associated with this. Currently, therefore, use of exogenous hormones does not offer a practical public health measure to prevent gynecological cancer. It is, however, possible that greater understanding of the relative risks and benefits of both estrogen and progesterone on the risks of cancer at different sites and the mechanisms underlying these effects, may eventually lead to development of hormone formulations or methods of administration that could be used to reduce risk of ovarian and endometrial cancers without adversely affecting risk of cancer at other sites.

It has been estimated that approximately 37% of endometrial and 21% of ovarian cancers in the UK are attributable to lifestyle and environmental factors that are amenable to change [77]. In particular, approximately one third of endometrial cancers could potentially be prevented if no women were overweight or 4% if women were more physically active [77]. Furthermore, the limited data looking at the effects of weight loss suggest that women who are already obese would benefit from losing weight [51,52]. In the UK, a lack of breastfeeding accounted for the greatest proportion of ovarian cancers, approximately 18% [77]. It is important, however, to note that this estimate was based on a relatively low prevalence of breastfeeding in the UK and the assumption that risk was reduced by 2% per month of

breastfeeding. Other studies suggest an estimate of up to 1% per month may be more realistic [36,37] thus the potential benefits of increasing breastfeeding may be considerably lower, especially in countries where breastfeeding is already a common practice. The UK study did not consider obesity as a potential cause of ovarian cancer but, with increasing evidence of a link, it is possible that reducing the prevalence of obesity would also reduce incidence of ovarian cancer. In the UK study, approximately 3% of cases of ovarian cancer were attributed to smoking although the cancers that are associated with both obesity and smoking are generally the less aggressive subtypes thus while intervention might reduce incidence rates, it is unlikely to have much effect on mortality.

## SURVIVAL AFTER A DIAGNOSIS OF GYNECOLOGICAL CANCER

As more women are diagnosed with gynecological cancer there is increasing demand for information about environmental or lifestyle factors that might improve survival, particularly for women with ovarian cancer where 5-year survival rates are still less than 45% [103]. To date this area has not attracted much research attention and the data currently available come primarily from cohorts of patients who have participated in case-control studies of etiology and been followed up for mortality to see whether aspects of their lifestyle prior to diagnosis are associated with survival.

The factor that has been studied most extensively in relation to cancer outcomes in general is physical activity with most studies suggesting that increased activity is associated with higher quality of life during treatment and lower recurrence rates and mortality after treatment has ended [78]. Although there are currently few data for gynecological cancers, it seems likely that similar benefits will be seen.

The area that has attracted most attention in relation to gynecological cancer is that of obesity. A recent meta-analysis suggested that greater body-size is associated with a poorer

outcome for women with ovarian cancer, with obese women having a 17% greater risk of dying than their normal-weight counterparts [79]. Possible reasons for this difference are that obese women may develop inherently more aggressive cancers, or the practice of capping chemotherapy doses for obese women such that they are not given the full dose based on their body-size because of concerns regarding toxicity. There are, however, no data regarding the potential benefits (or otherwise) of advising women with ovarian cancer to lose weight and this will be a challenging area to address as unintentional weight loss is often a marker of advancing disease and thus a poor outcome. The relation between body-size and survival following a diagnosis of endometrial cancer is much less clear as most women do not die from their cancer. Thus while obese women are at greatly increased risk of developing endometrial cancer, they are more likely to develop low grade, early stage cancers that have an inherently good prognosis, but are at greatly increased risk of dying from other obesity-related causes in the longer term. Conversely, a higher proportion of cancers among normal weight women will be aggressive Type 2 cancers [15] that are more likely to prove fatal. There are currently no reliable data to draw any definitive conclusions regarding the influence of obesity on endometrial cancer-specific survival however, as most obese women with endometrial cancers will die from other causes, it is very likely that a recommendation to lose weight would improve both quality of life and survival in this group.

There is mounting evidence that diet after a diagnosis of cancer may play a role in determining individual patient outcomes but again few studies have assessed the relation for gynecological cancer although there are suggestions that increasing intake of fruit and/or vegetables [80,81], vitamin E [81] and green tea [82] may confer some benefit for women with ovarian cancer. However, with the exception of the latter study, the investigators have relied on information about diet prior to diagnosis and could not allow for dietary change after

diagnosis. The greatest evidence for an association between diet after diagnosis and cancer outcomes comes from the breast and colorectal cancer fields where observational studies have suggested that a number of aspects of diet might be associated with survival, although the two trials conducted to date have not shown consistent benefits for women with breast cancer randomized to a low-fat [83] or low-fat and high vegetables, fruit and fiber diet [84]. Further support comes from a study showing that breast cancer survivors who ate a more healthy diet according to the US Healthy Eating Index had lower circulating levels of C-reactive protein (CRP), a marker of inflammation [85] and lower CRP levels have been associated with improved breast cancer survival [86]. However, it may not be valid to extrapolate results from studies of breast cancer to ovarian cancer because a much higher proportion of breast cancer survivors die from non-cancer causes. Although many cancer survivors take dietary supplements, there is currently no evidence to suggest that these are associated with improved outcomes [78].

## CONCLUSION

Although our knowledge of risk factors for gynecological cancer is increasing (Table 1), the strongest associations are with reproductive or hormonal exposures that are either not amenable to intervention or have the opposite effect on risk of breast cancer. Weight control would have a major impact on risk of endometrial cancer and, probably, the less aggressive subtypes of ovarian cancer, although any impact on mortality from these cancers is likely to be more limited. Other standard health recommendations such as increasing physical activity and smoking cessation are likely to reduce risk of some types of gynecological cancer, while avoidance of talcum powder in the perineal region may have a modest effect on ovarian cancer risk. There is currently insufficient evidence to draw any strong conclusions regarding the potential of factors such as diet and use of aspirin; further evidence is also required

494 regarding the potential for lifestyle choices to influence survival following a diagnosis of
495 gynecological cancer.

496

497

Reference annotations:

#15: *Large pooled analysis evaluating risk factors separately for type 1 and type 2 endometrial cancers.

#22: *Large pooled analysis evaluating relation between oral contraceptive pill use and ovarian cancer risk.

#25: *Large pooled analysis evaluating relation between oral contraceptive pill use and cervical cancer risk.

#38: **Updated report from the World Cancer Research Fund and American Institute of Cancer Research summarizing the evidence for a causal role of food, nutrition and physical activity in the etiology of ovarian cancer.

#39: **Updated report from the World Cancer Research Fund and American Institute of Cancer Research summarizing the evidence for a causal role of food, nutrition and physical activity in the etiology of endometrial cancer.

#53: *Large pooled analysis evaluating relation between body-size and ovarian cancer risk.

#61: *Large pooled analysis evaluating relation between smoking and ovarian cancer.

#76: **Summary of a series of reports evaluating the proportions of common cancers attributable to potentially modifiable risk factors in the UK.

#79: *Meta-analysis of the association between body-size and survival from ovarian cancer.

## References

1. Gilks CB, Prat J: Ovarian carcinoma pathology and genetics: recent advances. *Hum Pathol* 40(9), 1213-1223 (2009).
2. Tothill RW, Tinker AV, George J *et al.*: Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. *Clin Cancer Res* 14(16), 5198-5208 (2008).
3. Chen VW, Ruiz B, Killeen JL, Cote TR, Wu XC, Correa CN: Pathology and classification of ovarian tumors. *Cancer* 97(10 Suppl), 2631-2642 (2003).
4. Fasching PA, Gayther S, Pearce L *et al.*: Role of genetic polymorphisms and ovarian cancer susceptibility. *Mol Oncol* 3(2), 171-181 (2009).
5. Bonadona V, Bonaiti B, Olschwang S *et al.*: Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA : the journal of the American Medical Association* 305(22), 2304-2310 (2011).
6. Bouvard V, Baan R, Straif K *et al.*: A review of human carcinogens--Part B: biological agents. *Lancet Oncol* 10(4), 321-322 (2009).
7. Jordan SJ, Nagle CM, Coory MD *et al.*: Has the association between hysterectomy and ovarian cancer changed over time? A systematic review and meta-analysis. *European journal of cancer* 49(17), 3638-3647 (2013).
8. Sieh W, Salvador S, Mcguire V *et al.*: Tubal ligation and risk of ovarian cancer subtypes: a pooled analysis of case-control studies. *Int J Epidemiol* 42(2), 579-589 (2013).
9. Pearce C, Templeman C, Rossing M *et al.*: Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case–control studies. *Lancet Oncology* 13, 385-394 (2012).
10. Rowlands IJ, Nagle CM, Spurdle AB, Webb PM: Gynecological conditions and the risk of endometrial cancer. *Gynecol Oncol* 123(3), 537-541 (2011).

11. Friberg E, Orsini N, Mantzoros CS, Wolk A: Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia* 50(7), 1365-1374 (2007).

12. Fearnley EJ, Marquart L, Spurdle AB, Weinstein P, Webb PM: Polycystic ovary syndrome increases the risk of endometrial cancer in women aged less than 50 years: an Australian case-control study. *Cancer Causes Control* 21(12), 2303-2308 (2010).

13. Dossus L, Allen N, Kaaks R *et al.*: Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*, (2009).

14. Tsilidis KK, Allen NE, Key TJ *et al.*: Oral contraceptive use and reproductive factors and risk of ovarian cancer in the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer* 105, 1436-1422 (2011).

15. Setiawan VW, Yang HP, Pike MC *et al.*: Type I and II endometrial cancers: have they different risk factors? *J Clin Oncol* 31(20), 2607-2618 (2013).

16. Whittemore AS, Harris R, Itnyre J: Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol* 136(10), 1184-1203. (1992).

17. Moorman PG, Calingaert B, Palmieri RT *et al.*: Hormonal risk factors for ovarian cancer in premenopausal and postmenopausal women. *Am J Epidemiol* 167(9), 1059-1069 (2008).

18. Setiawan VW, Pike MC, Karageorgi S *et al.*: Age at last birth in relation to risk of endometrial cancer: pooled analysis in the epidemiology of endometrial cancer consortium. *Am J Epidemiol* 176(4), 269-278 (2012).

19. Neale RE, Purdie DM, Murphy MF, Mineau GP, Bishop T, Whiteman DC: Twinning and the incidence of breast and gynecological cancers (United States). *Cancer Causes Control* 15(8), 829-835 (2004).

20. Whiteman DC, Murphy MF, Cook LS *et al.*: Multiple births and risk of epithelial ovarian cancer. *Journal of the National Cancer Institute* 92(14), 1172-1177 (2000).

21. International Collaboration of Epidemiological Studies of Cervical Cancer: Cervical carcinoma and reproductive factors: collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies. *Int J Cancer* 119(5), 1108-1124 (2006).

22. International Collaboration of Epidemiological Studies of Cervical Cancer: Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. *Int J Cancer* 120(4), 885-891 (2007).

23. Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Doll R, Hermon C, Peto R, Reeves G: Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet* 371(9609), 303-314 (2008).

24. Mueck AO, Seeger H, Rabe T: Hormonal contraception and risk of endometrial cancer: a systematic review. *Endocr Relat Cancer* 17(4), R263-271 (2010).

25. International Collaboration of Epidemiological Studies of Cervical Cancer, Appleby P, Beral V *et al.*: Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. *Lancet* 370(9599), 1609-1621 (2007).

26. Beral V, Bull D, Reeves G: Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 365(9470), 1543-1551 (2005).

27. De Villiers TJ, Pines A, Panay N *et al.*: Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. *Climacteric : the journal of the International Menopause Society* 16(3), 316-337 (2013).

28. Beral V, Bull D, Green J, Reeves G: Ovarian cancer and hormone replacement therapy in the Million Women Study. *Lancet* 369(9574), 1703-1710 (2007).

29. Tsilidis KK, Allen NE, Key TJ *et al.*: Menopausal hormone therapy and risk of ovarian cancer in the European prospective investigation into cancer and nutrition. *Cancer Causes Control* 22(8), 1075-1084 (2011).

30. Brinton LA, Felix AS: Menopausal hormone therapy and risk of endometrial cancer. *The Journal of steroid biochemistry and molecular biology*, (2013).

31. Anderson GL, Judd HL, Kaunitz AM *et al.*: Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA : the journal of the American Medical Association* 290(13), 1739-1748 (2003).

32. Anderson GL, Limacher M, Assaf AR *et al.*: Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA : the journal of the American Medical Association* 291(14), 1701-1712 (2004).

33. Dhar KK, Needhirajan T, Koslowski M, Woolas RP: Is levonorgestrel intrauterine system effective for treatment of early endometrial cancer? Report of four cases and review of the literature. *Gynecologic Oncology* 97(3), 924-927 (2005).

34. Seeber B, Ziehr SC, Gschliebetaer A *et al.*: Quantitative levonorgestrel plasma level measurements in patients with regular and prolonged use of the levonorgestrel-releasing intrauterine system. *Contraception* 86(4), 345-349 (2012).

35. Jordan SJ, Siskind V, A CG, Whiteman DC, Webb PM: Breastfeeding and risk of epithelial ovarian cancer. *Cancer Causes Control* 21(1), 109-116 (2010).

36. World Cancer Research Fund/American Institute for Cancer Research: Food, nutrition, physical activity, and the prevention of cancer:a global perspective. (2007).

617 37. Luan NN, Wu QJ, Gong TT, Vogtmann E, Wang YL, Lin B: Breastfeeding and ovarian
618 cancer risk: a meta-analysis of epidemiologic studies. *The American journal of clinical*
619 *nutrition* 98(4), 1020-1031 (2013).
620 38. World Cancer Research Fund /American Institute for Cancer Research Continuous Update
621 Project Report: Food, Nutrition, Physical Activity, and the Prevention of Ovarian Cancer.
622 (http://www.dietandcancerreport.org/cup/cup_resources.php), (2014).
623 39. World Cancer Research Fund /American Institute for Cancer Research Continuous Update
624 Project Report: Food, Nutrition, Physical Activity, and the Prevention of Endometrial Cancer.
625 (Available at http://www.dietandcancerreport.org.), (2013).
626 40. Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG: Ovarian tumors in a cohort of
627 infertile women. *N Engl J Med* 331(12), 771-776 (1994).
628 41. Jensen A, Sharif H, Frederiksen K, Kjaer SK: Use of fertility drugs and risk of ovarian
629 cancer: Danish Population Based Cohort Study. *BMJ* 338, b249 (2009).
630 42. Brinton LA, Westhoff CL, Scoccia B *et al.*: Fertility drugs and endometrial cancer risk:
631 results from an extended follow-up of a large infertility cohort. *Hum Reprod* 28(10), 2813-
632 2821 (2013).
633 43. Jensen A, Sharif H, Kjaer SK: Use of fertility drugs and risk of uterine cancer: results from a
634 large Danish population-based cohort study. *Am J Epidemiol* 170(11), 1408-1414 (2009).
635 44. Brinton LA, Trabert B, Shalev V, Lunenfeld E, Sella T, Chodick G: In vitro fertilization and
636 risk of breast and gynecologic cancers: a retrospective cohort study within the Israeli Maccabi
637 Healthcare Services. *Fertility and sterility* 99(5), 1189-1196 (2013).
638 45. Finucane MM, Stevens GA, Cowan MJ *et al.*: National, regional, and global trends in body-
639 mass index since 1980: systematic analysis of health examination surveys and
640 epidemiological studies with 960 country-years and 9.1 million participants. *Lancet*
641 377(9765), 557-567 (2011).

642 46. Key TJ, Allen NE, Verkasalo PK, Banks E: Energy balance and cancer: the role of sex
643 hormones. *The Proceedings of the Nutrition Society* 60(1), 81-89 (2001).
644 47. Parekh N, Okada T, Lu-Yao GL: Obesity, insulin resistance, and cancer prognosis:
645 implications for practice for providing care among cancer survivors. *J Am Diet Assoc* 109(8),
646 1346-1353 (2009).
647 48. Crosbie E, Zwahlen M, Kitchener H, Egger M, Renehan AG: Body mass index, hormone
648 replacement therapy and endometrial cancer risk: a meta-analysis. *Cancer Epidemiol*
649 *Biomarkers Prev* 19(12), 3119-3130 (2010).
650 49. Bjorge T, Engeland A, Tretli S, Weiderpass E: Body size in relation to cancer of the uterine
651 corpus in 1 million Norwegian women. *Int J Cancer* 120(2), 378-383 (2007).
652 50. Yang HP, Wentzensen N, Trabert B *et al.*: Endometrial Cancer Risk Factors by 2 Main
653 Histologic Subtypes: The NIH-AARP Diet and Health Study. *Am J Epidemiol*, (2012).
654 51. Trentham-Dietz A, Nichols H, Hampton J, Newcomb P: Weight change and risk of
655 endometrial cancer. *International Journal of Epidemiology* 35, 151-158 (2006).
656 52. Nagle C, Marquart L, Bain C *et al.*: Impact of weight change and weight cycling on risk of
657 different subtypes of endometrial cancer. *European journal of cancer* 49(12), 2717-2726
658 (2013).
659 53. Collaborative Group on Epidemiological Studies of Ovarian Cancer: Ovarian cancer and body
660 size: individual participant meta-analysis including 25157 women with ovarian cancer from
661 47 epidemiological studies. *PLoS Medicine* 9(4), e1001200 (2012).
662 54. Olsen CM, Nagle C, Whiteman DC *et al.*: Obesity and risk of ovarian cancer subtypes:
663 evidence from the Ovarian Cancer Association Consortium. *Endocr Relat Cancer* 20(2), 251-
664 262 (2013).
665 55. Olsen CM, Bain CJ, Jordan SJ *et al.*: Recreational physical activity and epithelial ovarian
666 cancer: a case-control study, systematic review, and meta-analysis. *Cancer Epidemiol*
667 *Biomarkers Prev* 16(11), 2321-2330 (2007).

668 56. Crane TE, Khulpateea BR, Alberts DS, Basen-Engquist K, Thomson CA: Dietary Intake and
669 Ovarian Cancer Risk: A Systematic Review. *Cancer Epidemiol Biomarkers Prev*, (2013).
670 57. Braem MG, Onland-Moret NC, Schouten LJ *et al.*: Coffee and tea consumption and the risk
671 of ovarian cancer: a prospective cohort study and updated meta-analysis. *The American*
672 *journal of clinical nutrition* 95(5), 1172-1181 (2012).
673 58. Butler LM, Wu AH: Green and black tea in relation to gynecologic cancers. *Molecular*
674 *nutrition & food research* 55(6), 931-940 (2011).
675 59. Nagle CM, Olsen CM, Bain CJ, Whiteman DC, Green AC, Webb PM: Tea consumption and
676 risk of ovarian cancer. *Cancer Causes Control* 21(9), 1485-1491 (2010).
677 60. International Collaboration of Epidemiological Studies of Cervical Cancer, Appleby P, Beral
678 V *et al.*: Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual
679 data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of
680 the cervix from 23 epidemiological studies. *Int J Cancer* 118(6), 1481-1495 (2006).
681 61. Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Gaitskell K *et*
682 *al.*: Ovarian cancer and smoking: individual participant meta-analysis including 28,114
683 women with ovarian cancer from 51 epidemiological studies. *Lancet Oncol* 13(9), 946-956
684 (2012).
685 62. Faber MT, Kjaer SK, Dehlendorff C *et al.*: Cigarette smoking and risk of ovarian cancer: a
686 pooled analysis of 21 case-control studies. *Cancer Causes Control* 24(5), 989-1004 (2013).
687 63. Zhou B, Yang L, Sun Q *et al.*: Cigarette smoking and the risk of endometrial cancer: a meta-
688 analysis. *The American journal of medicine* 121(6), 501-508 e503 (2008).
689 64. Tanko LB, Christiansen C: An update on the antiestrogenic effect of smoking: a literature
690 review with implications for researchers and practitioners. *Menopause* 11(1), 104-109 (2004).
691 65. Fedirko V, Jenab M, Rinaldi S *et al.*: Alcohol drinking and endometrial cancer risk in the
692 European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Annals of*
693 *epidemiology* 23(2), 93-98 (2013).

66. Kelemen LE, Bandera EV, Terry KL *et al.*: Recent alcohol consumption and risk of incident ovarian carcinoma: a pooled analysis of 5,342 cases and 10,358 controls from the Ovarian Cancer Association Consortium. *BMC Cancer* 13, 28 (2013).

67. Neill AS, Nagle CM, Protani MM, Obermair A, Spurdle AB, Webb PM: Aspirin, nonsteroidal anti-inflammatory drugs, paracetamol and risk of endometrial cancer: A case-control study, systematic review and meta-analysis. *Int J Cancer* 132(5), 1146-1155 (2012).

68. Brasky TM, Moysich KB, Cohn DE, White E: Non-steroidal anti-inflammatory drugs and endometrial cancer risk in the VITamins And Lifestyle (VITAL) cohort. *Gynecol Oncol* 128(1), 113-119 (2013).

69. Setiawan VW, Matsuno RK, Lurie G *et al.*: Use of nonsteroidal anti-inflammatory drugs and risk of ovarian and endometrial cancer: the Multiethnic Cohort. *Cancer Epidemiol Biomarkers Prev* 21(9), 1441-1449 (2012).

70. Trabert B, Ness RB, Lo-Ciganic WH *et al.*: Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium. *Journal of the National Cancer Institute* 106(2), djt431 (2014).

71. Baandrup L, Faber MT, Christensen J *et al.*: Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. *Acta obstetricia et gynecologica Scandinavica* 92(3), 245-255 (2013).

72. Wilson JC, O'rorke MA, Cooper JA *et al.*: Non-steroidal anti-inflammatory drug use and cervical cancer risk: A case-control study using the Clinical Practice Research Datalink. *Cancer epidemiology* 37(6), 897-904 (2013).

73. Terry KL, Karageorgi S, Shvetsov YB *et al.*: Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer prevention research* 6(8), 811-821 (2013).

74. Crawford L, Reeves KW, Luisi N, Balasubramanian R, Sturgeon SR: Perineal powder use and risk of endometrial cancer in postmenopausal women. *Cancer Causes Control* 23(10), 1673-1680 (2012).

75. Neill AS, Nagle CM, Spurdle AB, Webb PM: Use of talcum powder and endometrial cancer risk. *Cancer Causes Control* 23(3), 513-519 (2012).

76. Parkin DM: 10. Cancers attributable to exposure to hormones in the UK in 2010. *Br J Cancer* 105 Suppl 2, S42-48 (2011).

77. Parkin DM, Boyd L, Walker LC: 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. *Br J Cancer* 105 Suppl 2, S77-81 (2011).

78. Rock CL, Doyle C, Demark-Wahnefried W *et al.*: Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin* 62(4), 242-274 (2012).

79. Protani MM, Nagle CM, Webb PM: Obesity and ovarian cancer survival: a systematic review and meta-analysis. *Cancer prevention research* 5(7), 901-910 (2012).

80. Dolecek TA, Mccarthy BJ, Joslin CE *et al.*: Prediagnosis Food Patterns Are Associated with Length of Survival from Epithelial Ovarian Cancer. *J Am Diet Assoc* 110(3), 369-382 (2010).

81. Nagle CM, Purdie DM, Webb PM, Green A, Harvey PW, Bain CJ: Dietary influences on survival after ovarian cancer. *Int J Cancer* 106(2), 264-269 (2003).

82. Zhang M, Lee AH, Binns CW, Xie X: Green tea consumption enhances survival of epithelial ovarian cancer. *Int J Cancer* 112(3), 465-469 (2004).

83. Chlebowski RT, Blackburn GL, Thomson CA *et al.*: Dietary fat reduction and breast cancer outcome: interim efficacy results from the Women's Intervention Nutrition Study. *Journal of the National Cancer Institute* 98(24), 1767-1776 (2006).

84. Pierce JP, Natarajan L, Caan BJ *et al.*: Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. *J Am Med Assoc* 298(3), 289-298 (2007).

744 85. George SM, Neuhouser ML, Mayne ST *et al.*: Postdiagnosis diet quality is inversely related
745 to a biomarker of inflammation among breast cancer survivors. *Cancer Epidemiol Biomarkers*
746 *Prev* 19(9), 2220-2228 (2010).
747 86. Pierce BL, Ballard-Barbash R, Bernstein L *et al.*: Elevated biomarkers of inflammation are
748 associated with reduced survival among breast cancer patients. *J Clin Oncol* 27(21), 3437-
749 3444 (2009).

750

751 **Websites**

752 101. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin
753 DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality
754 Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency
755 for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 15
756 December 2013.
757 102. Forman D, Bray F, Brewster DH, Gombe Mbalawa C, Kohler B, Piñeros M,
758 Steliarova-Foucher E, Swaminathan R and Ferlay J eds (2013). Cancer Incidence in
759 Five Continents, Vol. X (electronic version) Lyon, IARC. http://ci5.iarc.fr accessed
760 on 15 December 2013.
761 103. Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary
762 CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ,
763 Cronin KA (eds). SEER Cancer Statistics Review, 1975-2010, National Cancer
764 Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2010/, based on November
765 2012 SEER data submission, posted to the SEER web site, April 2013. Accessed on 6
766 January 2014.

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769 **Table 1. A summary of risk factors for endometrial, ovarian and cervical cancer**

| | Endometrial Cancer | Ovarian Cancer | Cervical Cancer |
|---|---|---|---|
| **Medical history** | | | |
| HPV infection | | | Necessary |
| Hysterectomy | ↓↓↓ | ? | |
| Tubal sterilisation | | ↓ | |
| Endometriosis | – | ↑ CCC & END | |
| Diabetes | ↑ | | |
| Polycystic ovary syndrome | ↑ | | |
| **Reproductive history & hormones** | | | |
| Older age at menarche | ↓ | – | |
| Younger age at menopause | ↓ | ↓ | |
| Parity | ↓↓↓ | ↓↓↓ | ↑ |
| Breastfeeding | – | ↓ | |
| Oral contraceptive pill | ↓↓↓ | ↓↓↓ | ↑ (Recent use) |
| Hormone replacement therapy: | | | |
| Estrogen-only | ↑↑↑ | ↑↑ | |
| Combined E + P | ↓? (Continuous) | ↑ | |
| Fertility drugs | –? | –? | –? |
| **Lifestyle** | | | |
| Overweight & obesity | ↑↑↑ | ↑ (not SER?) | – |
| Physical activity | ↓ | ? | |
| Diet | ↑ Glycemic index | ? | |
| Coffee | ↓ Coffee | - | |
| Tea | ↓? Green tea | ↓? Green tea | |
| Smoking | ↓ | ↑↑ MUC | ↑ |
| Alcohol | – | – | |
| NSAIDs | ↓? | ? | |
| Talcum powder | –? | ↑ | ` |

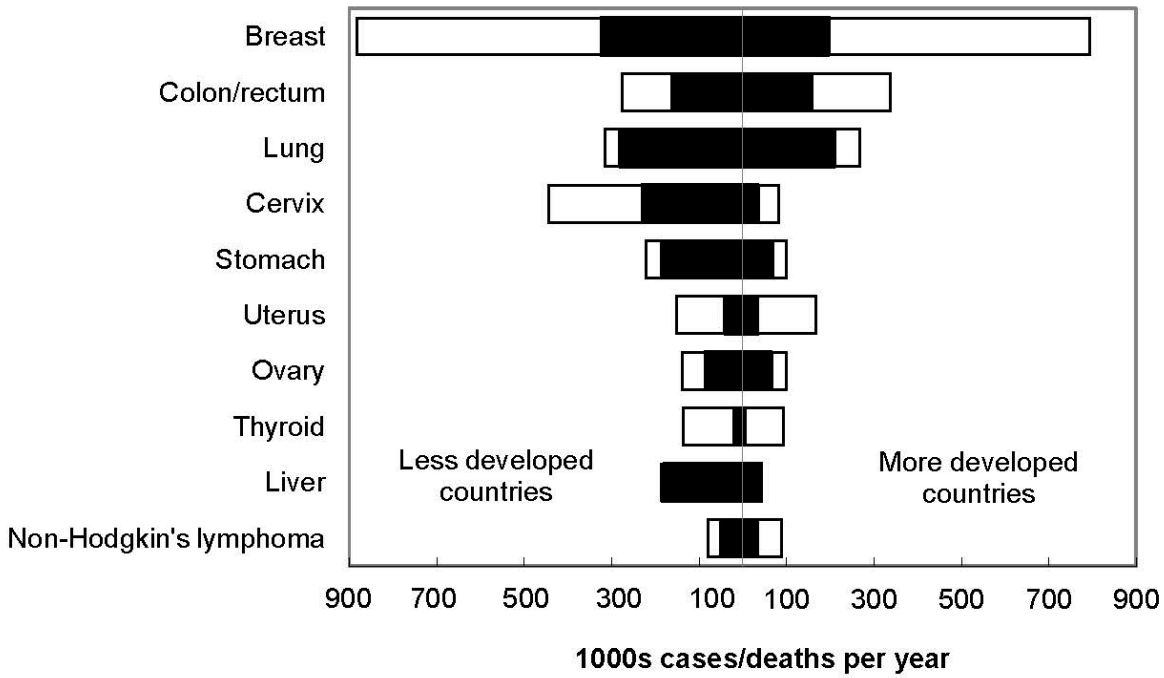
770 Abbreviations: CCC, clear cell cancer; END, endometrioid cancer, ERT, estrogen
771 replacement therapy; MUC, mucinous cancer; NSAIDs, nonsteroidal anti-inflammatory
772 drugs; SER, serous cancer

773 *↑/↓ = increased/decreased risk; number of arrows indicates the strength of the association; –
774 = no evidence for an association; ? = some evidence for association/lack of association but
775 not confirmed.

776

777 **Figure 1.** Numbers of new cases (white bars) and deaths (black bars) per year for the ten
778 most common cancers in women worldwide, by level of economic development (drawn from
779 GLOBOCAN data [101])

780

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