Risk factors and risk reduction of breast and ovarian cancer
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Purpose of review
Breast and ovarian cancer remain a significant burden for women living in the Western world. This paper reviews the risk factors and current strategies to prevent these diseases.

Recent findings
Established factors associated with the risk of breast cancer include family history, reproductive factors and lactation, as well as age at menarche and menopause. Hormone replacement therapy increases the risk, whereas oral contraceptives probably confer no increased risk. Alcohol moderately increases the risk, whereas a diet rich in folate and carotenoids might be protective. The role of other dietary factors, smoking and physical exercise remain unclear. Important risk factors for ovarian cancer are reproductive factors and possibly the long-term use of hormone replacement therapy. The risk is decreased by oral contraceptives. In carriers of a *BRCA1* or *BRCA2* gene mutation, prophylactic surgery can significantly reduce the risk of breast as well as ovarian cancer. Tamoxifen may be considered as a chemopreventive agent in women with a high risk of breast cancer, including carriers of a *BRCA2* mutation, but is probably not effective in *BRCA1* carriers.

Summary
During the period of this review, the importance of several known risk factors was confirmed, whereas the effects of other factors became more clear. Chemoprevention and prophylactic surgery have emerged as preventative options that can reduce the risk of breast and ovarian cancer.

Keywords
breast cancer, ovarian cancer, prevention, review, risk factors

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Introduction
This paper reviews recent studies (mainly published since July 2001) on risk factors and risk-reducing strategies for breast and ovarian cancer. The effectiveness of screening for breast and ovarian cancer is not considered in this review and will be discussed elsewhere.

Breast cancer
Breast cancer remains the most frequent type of cancer in women in the world with nearly 1 million new cases each year worldwide. In most developed countries the incidence levels are levelling off and, very recently, declining in some countries, especially in women under the age of 40 years [1].

With a total of 375 000 deaths each year, it is also the leading cause of cancer mortality in Europe, and the second in the United States only after lung cancer [2,3]. Mortality figures have been declining for a number of years now, and this trend continues, most likely by a combination of early detection and improved treatment [3].

Risk factors
Breast cancer is a hormonally related process; most breast cancer risk factors act through changes in hormonal (mainly oestrogen) levels that influence the breast epithelium.

Familial breast cancer
Family history is the most important breast cancer risk factor. Approximately 5% of all breast cancers are caused by germline mutations in the *BRCA1* and *BRCA2* genes.

Evidence of a third breast cancer predisposition gene was found by a combined investigation of Dutch and British researchers. They found that mutations in *CHEK-2*, a gene involved in DNA repair, account for approximately 1% of all breast cancers. The clinical application is still limited as segregation analysis suggests that the mutation is only expressed in combination with another, as yet unknown, gene mutation [4••].

Furthermore, two recurrent *ATM* mutations might be associated with a nearly 16-fold increased risk compared with the general population [5••].

Other genetic and environmental factors probably further modify the risk. A recent review [6] found an

association for 13 polymorphisms in 10 genes. In addition, findings from a genetic modelling study [7•] suggested that several low-penetrance genes rather than one 'BRCA3' gene account for the residual familial aggregation of breast cancer.

Reproductive factors

Age at first childbirth, parity and age at menarche are well-known factors that are associated with the risk of breast cancer. Their strength varies with age at diagnosis [8].

Placental characteristics might play a role: a large follow-up study [9•], which started more than 40 years ago, provided evidence that smaller placentas, maternal floor infarction and increasing blood pressure during pregnancy all reduced the risk of breast cancer. The protective effect of pre-eclampsia, another marker of compromised placental function, was already known. A case–control study in 66 pregnancies with severe pre-eclampsia and 610 controls [10] suggested that the possible mechanism might be high levels of alpha-fetoprotein rather than low levels of oestradiol.

A history of induced abortion appears to have little influence on the risk of breast cancer, at least in Chinese women [11].

The effect of breast feeding has long been unclear but now appears to be firmly established: in addition to several individual studies, a collaborative re-analysis of data from 47 studies with a total of 50 302 women with breast cancer and 96 973 healthy women showed that the relative risk of breast cancer decreased by 4.3% for each year of breast feeding [12•].

Oral contraceptives

The risk of oral contraceptive usage appeared to be clearly established, with numerous case–control and cohort studies showing a small increased risk of breast cancer with long-term usage of oral contraceptives, especially at a young age. However, a very large study was recently published that found no association between current or past use of oral contraceptives and breast cancer. The study was, with 4575 breast cancer cases and 4682 controls, large enough to perform subgroup analyses with respect to long duration of use, a high dosage of oestrogens, initation at a young age, or a family history of breast cancer. None of these subgroups had a significantly increased risk [13••].

Hormone replacement therapy

Much publicity was gained by the publication of the Women's Health Initiative (WHI) randomized controlled trial, in which women were randomly assigned between receiving oestrogens plus medroxyprogester-

one acetate ($n = 8506$) or placebo ($n = 8102$). In addition to an excess of cardiovascular disease, the risk of breast cancer was increased in the treatment arm [hazard ratio (HR) 1.27; 95% confidence interval (CI) 1.00–1.59]. The trial was terminated early [14••]. The results are consistent with the (non-significant) 27% increase found in the Heart and Estrogen Replacement Study II in postmenopausal women with coronary disease [15] and estimates from numerous observational studies suggesting an increased risk, especially of current long-term use (>5 years).

Benign breast disease

The assocation between proliferative breast lesions, especially atypical hyperplasia, and breast cancer has long been recognized. The risk of breast cancer in patients with atypical hyperplasia is approximately equal in both breasts. Furthermore, the pathological features of breast cancers developing in women with benign breast disease, including atypical hyperplasia, do not vary according to the histology of the previous benign breast lesion [16]. Together, these findings suggest that these lesions are risk indicators rather than direct precursors of breast cancer.

Alcohol and diet

In agreement with many previous studies, a large prospective study with 1328 incident cases of breast cancer found that alcohol use moderately increased the risk of breast cancer [17]. Although the assocation with the 'western' diet (characterized by meat, fat, dairy and sweets) remains unconfirmed [17,18], a number of other factors are now consistently associated with the risk of breast cancer; carotenoids decrease the risk [19] as well as folate [20]. The risk of low folate intake is more increased in combination with alcoholic beverages [21].

A decreased risk of soy (phytoestrogens) has only been established in Chinese women; a case–control study in Shanghai [22] suggested that regular soy consumption reduced the risk of breast cancer, especially for ER/PR-positive tumours. In non-Asian women phytoestrogens appeared to have little effect [23].

Smoking

Until recently, studies into the role of active and passive smoking failed to show an effect of smoking on the risk of breast cancer. It might be that the contrast in the comparison of ever versus never smokers was insufficient. Data from the Nurses' Health Study were compatible with a small increased risk of active smoking, with the highest risks in women initiating smoking before the age of 17 years. No association with passive smoking was found [24].

Anthropometry

It is well known that height and weight are related to breast cancer. The assocation with weight differs according to menopausal status. Whereas leanness is positively associated with premenopausal breast cancer, overweight (especially visceral) increases the risk of postmenopausal breast cancer. This was confirmed in a Canadian case–control study of 1233 incident breast cancer cases and 1241 controls: a larger waist–hip ratio and weight gain increase the risk of postmenopausal breast cancer [25]. Both a Finnish cohort study in 3447 women and a pooled analysis of four case–control studies [26,27] suggested that the risk of premenopausal breast cancer is affected early in life; a positive association was found for tallness during childhood whereas a negative association was found with body mass index at a young age.

Physical activity

The evidence remains inconsistent; a case–control study of 1237 incident cases and 1241 controls suggested that sustained physical activity throughout life and particularly later in life moderately reduced the risk of breast cancer [28]. On the other hand, a case–control study of 394 cases and 788 controls showed no assocation with lifetime physical activity [29]. The reasons for this inconsistency might be different assessment methods of physical activity or interaction with other factors. This is suggested by a Swedish cohort study [30] that found an association with physical activity only for normal-weight postmenopausal and overweight premenopausal women.

Environmental factors

A Canadian case–control study found an association with dioxin-like polychlorinated biphenyls, suggesting that exposure to these substances might increase the risk of breast cancer or, alternatively, that cases and controls have different metabolic pathways involved in the biotransformation of polychlorinated biphenyls and oestrogens [31]. P53 mutations might modify this association [32].

Two studies, a case–control and a cohort [33•,34•], were published that found a positive association between the disruption of the diurnal sleep–wakefulness rhythm, especially during night-shift work and the risk of breast cancer. The mechanism is unclear but is postulated to be exposure to light at night, causing a reduced level of melatonin, a hormone that suppresses ovarian oestrogen production.

Chronic exposure to residential magnetic fields might also suppress the nocturnal production of melatonin. However, no assocation was found in a recent case–control study with 813 cases and 793 age-matched controls [35].

Ovarian cancer

Epithelial ovarian cancer is the seventh most frequent cancer in European women, with 58 000 new cases and 38 000 deaths in 1995 [36]. The incidence is low under the age of 40 years but increases rapidly after menopause. Despite new chemotherapy agents, the prognosis remains fairly poor with a 5-year relative survival of 30% [37].

Risk factors

Many theories have been postulated regarding the pathogenesis of ovarian cancer. Risk factors are not well defined, with the exception of parity and oral contraceptive use. Most studies consider the epidemiology of epithelial ovarian cancer, representing approximately 90% of all ovarian carcinomas.

Hereditary ovarian cancer

Approximately 10% of ovarian cancers are hereditary, with *BRCA1* and *BRCA2* explaining the majority (approximately 90%) of hereditary ovarian cancer cases. The lifetime risk varies between 15 and 66%, suggesting the existence of modifying genetic or environmental factors [38].

Reproductive factors

The protective effects of increasing parity and breast feeding have been clearly established. Early age at menarche and late age at menopause increase the risk of ovarian cancer only modestly, so that it can be assumed that the length of menstrual life plays no crucial role in the pathogenesis of the disease [39].

The risk of sub/infertility on the risk of ovarian cancer has been extensively studied. Most studies use attendance at an infertility clinic as a marker for subfertility. The difficulty is the differentiation between the infertility itself and the treatment given at the clinic, that may in itself increase the risk of ovarian cancer. A pooled analysis of case–control studies, including 5207 cases and 7705 controls, suggested that specific biological causes of infertility rather than fertility drugs increased the risk of ovarian cancer [40•].

Oral contraceptives

Several studies have consistently shown a decreased risk of sporadic as well as familial ovarian cancer [41]. The risk reduction is already apparent after a few months of use and persists for years after discontinuation. Low-dose formulations (<35 μg ethinyl oestradiol) also confer a substantial risk reduction [42]. However, inconsistent results were reported for women at risk of hereditary ovarian cancer. Although a case–control study in 207 *BRCA1/2* carriers [43] reported a significant 50% risk reduction, a case–control study in Jewish women [44•] found that oral contraceptives significantly

decreased the risk of ovarian cancer only in non-carriers but not in carriers of a *BRCA1/2* mutation.

Oestrogen/hormone replacement therapy

Hormone replacement therapy (HRT) has been inconsistently linked to ovarian cancer. Recently, several prospective studies [45•,46•] consistently found a small increased risk, especially for long-term users of oestrogen replacement therapy. Sequentially rather than continuously added progestins might further increase the risk [47].

Diet

The evidence remains inconsistent; recent studies suggest that food items high in carotene and lycopene might decrease the risk [48], whereas red meat was associated with an elevated risk [49]. However, all positive studies were case–control studies, and a recent prospective study within the Nurses' Health Study found no association between the usage of vitamins/carotenoids and ovarian cancer [50]. It might be that (part of) the reported associations in previous studies were caused by the various types of bias (especially recall bias) that can occur in case–control studies.

Physical activity

It is hypothesized that recreational physical activity may reduce the risk of ovarian cancer by decreasing oestrogen levels. However, although this reduced risk was found by several studies, others found no or even a modest positive assocation. The most recent study [51], with 327 cases and 3129 controls, reported a small, non-significant, decrease in risk only for the highest category of recent vigorous activity.

Use of non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs increase apoptosis in ovarian cancer cell lines and can inhibit ovulation [52]. In observational studies, the association between commonly used anti-inflammatory drugs and ovarian cancer remains unclear. A Danish cohort study found no evidence of a protective effect of paracetamol [53], and a case–control study conducted in the USA concluded that, although non-significant, the observed risk estimates appeared to be compatible with a small decrease of risk by regular (more than three times a week for a period of at least 6 months) aspirin use [54].

Risk reduction

Options to reduce the risk of breast and ovarian cancer include life-style modification, prophylactic surgery and chemoprevention.

Life-style modification

Risk factors that are most amenable for primary prevention are dietary factors (including alcohol), smok-

ing and physical exercise. Although the impact on the risk of breast and ovarian cancer is either unclear or at best modest, a healthy life-style with the avoidance of smoking, moderate usage of alcohol, and physical exercise is advisable as it might also decrease the risk of a number of other diseases, such as other cancer types and cardiovascular disease.

Prophylactic surgery

The short-term potential of prophylactic mastectomy was clearly demonstrated by a prospective study in 139 *BRCA1/2* carriers. Within 3 years' follow-up, no cases of breast cancer appeared in 76 women opting for prophylactic mastectomy and eight occurred in 63 women opting for intensive surveillance [55••].

Two complementary studies in *BRCA1/2* gene mutation carriers demonstrated that prophylactic (salpingo-)oophorectomy can reduce the risk of hereditary ovarian as well as breast cancer. In a prospective study of 170 carriers with a mean follow-up of 2 years [56••], one woman developed peritoneal cancer and three breast cancer in the salpingo-oophorectomy group of 98 women. Three occult stage I gynaecological tumours were found at the time of prophylactic surgery. In the surveillance group of 72 women, five women developed ovarian or peritoneal cancer and eight developed breast cancer. The combined HR for breast and gynaecological cancer was 0.25 (95% CI 0.08–0.74).

In a multicentre retrospective study with a mean follow-up of almost 9 years [57••], 58 out of 292 carriers opting for surveillance developed ovarian cancer. Among 259 women undergoing prophylactic oophorectomy, two women developed primary peritoneal cancer (HR 0.04; 95% CI 0.01–0.16). In six women a stage I ovarian cancer was diagnosed at the time of surgery. Breast cancer was diagnosed in 60 out of 142 women opting for surveillance compared with 21 out of 99 women in the oophorectomy group, giving an HR of 0.47 (95% CI 0.29–0.77).

The risk-reducing potential of tubal ligation had already been shown in sporadic ovarian cancer. In addition, a matched case–control study in 232 *BRCA1/2* carriers with ovarian cancer and 232 carriers without the disease [58] showed that the adjusted odds ratio of developing ovarian cancer was 0.39 ($P = 0.002$) after tubal ligation. The biological mechanism is unclear; hypotheses include the reduction of ovarian blood supply or a decreased retrograde transport of potential carcinogens through the fallopian tubes.

Breast cancer chemoprevention

The effect of tamoxifen in reducing the short-term risk of oestrogen receptor-positive tumours is clearly estab-

lished. A meta-analysis including updated results of all four randomized trials showed a significant 38% reduction in the incidence of breast cancer [59]. Its chemopreventive potential in *BRCA1* mutation carriers, at increased risk of oestrogen receptor-negative tumours, is less clear. In a subgroup analysis of 19 *BRCA1/2* cases participating in the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (NSABP-P1), no reduction of breast cancer incidence in *BRCA1* carriers was observed [relative risk (RR) 1.67; 95% CI 0.41–8.0], whereas there was a suggestion of a benefit in *BRCA2* carriers (RR 0.38; 95% CI 0.06–1.56) [60•]. The small number of cases warrants replication in larger datasets. A modelling study estimating the potential impact of tamoxifen on *BRCA1/2* carriers [61] concluded that the benefit of tamoxifen is likely to be modest in *BRCA1* carriers and might be larger in *BRCA2* carriers. Future chemopreventive agents may include raloxifene, which is now being compared with tamoxifen in the STAR trial [59].

Ovarian cancer chemoprevention

Oral contraceptives substantially reduce the risk of sporadic ovarian cancer, so might be an effective chemopreventive agent in high-risk women. However, because of the inconsistent results in *BRCA1/2* carriers [43,44•], it is premature to consider oral contraceptives for the chemoprevention of hereditary ovarian cancer.

Conclusion

In the period covered in this review, the importance of several known risk factors for breast and ovarian cancer was confirmed, whereas the effects of lactation, some dietary factors and HRT became more clear. In contrast to previous concerns, oral contraceptives probably confer no increased risk of breast cancer.

The publication of several prospective studies on the potential of risk-reducing surgery in *BRCA1/2* carriers provides evidence facilitating decision-making on preventative strategies in these high-risk women.

Whereas tamoxifen and oral contraceptives may be considered as chemopreventive agents for the reduction of the risk of breast and ovarian cancer, respectively, their potential in reducing the risk of hereditary breast and ovarian cancer is still unclear.

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