



# A Review of Modifiable Risk Factors in Young Women for the Prevention of Breast Cancer

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**Abstract:** Breast cancer is the most common cancer diagnosis in women aged less than 40 years and the second most common cause of cancer death in this age group. Global rates of young onset breast cancer have risen steadily over the last twenty years. Although young women with breast cancer have a higher frequency of underlying pathogenic mutations in high penetrance breast cancer susceptibility genes (CSG) than older women, the vast majority of young breast cancer patients are not found to have a germline CSG mutation. There is therefore a need to inform young women regarding non-genetic breast cancer risk factors which have the potential to be influenced by changes in individual behaviour. A Pubmed search was performed using the search terms “young” or “early onset”, and “breast cancer” and “modifiable risk”. Titles and abstracts from peer-reviewed publications were screened for relevance. This review presents evidence for potentially modifiable risk factors of breast cancer risk in young women, including lifestyle factors (physical activity, body habitus, alcohol use, smoking, shift work and socioeconomic factors), reproductive and hormonal factors and iatrogenic risks. The extent to which these factors are truly modifiable is discussed and interactions between genetic and non-genetic risk factors are also addressed. Health care professionals have an opportunity to inform young women about breast health and risk when presenting at a “teachable moment”, including the benefits of physical activity and alcohol habits as risk factor. More focussed discussions regarding individual personal risk and benefit should accompany conversations regarding reproductive health and take into consideration both non-modifiable and iatrogenic BC risk factors.

**Keywords:** modifiable, risk factors, lifestyle, breast cancer, prevention, young

## Introduction

Globally, breast cancer (BC) is currently the most common cancer diagnosed in women below the age of 40, accounting for 244,000 cases per year.<sup>1</sup> It is also the second highest cause of cancer-related mortality in women aged 0–39 worldwide with 44,800 deaths per year.<sup>1</sup> Women under the age of 45 account for 11% of all BC diagnoses in the United States (US)<sup>2</sup> and 9% in the United Kingdom (UK).<sup>3</sup> Furthermore, there has been a 16% increase in the incidence of BC in women aged 25–49 years since the 1990s.<sup>3</sup>

Geographically, the cumulative risk of developing BC varies between countries: the highest cumulative risk for women aged less than 40 years is seen in Italy and France (0.9%), and lowest in India (0.26%) with the UK and US having a moderate level of risk (0.77% and 0.61%, respectively).<sup>1</sup>

Most young women are not eligible for asymptomatic breast screening and therefore present to clinicians with either personal breast symptoms or family-related

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concerns. Although young women with breast cancer have a higher frequency of underlying pathogenic mutations in high penetrance breast cancer susceptibility genes (CSGs) than older women, the vast majority of young breast cancer patients are not found to have a germline CSG mutation.<sup>4</sup> Therefore, modifiable risk factors for breast cancer should also receive attention in this age group.

Clinician–patient interactions during a breast clinic consultation may provide unique opportunities to educate patients about modifiable cancer risk factors, so-called “teachable moments”<sup>5</sup> These opportunities occur regardless of whether or not the patient receives a cancer diagnosis<sup>6</sup> and consultations pertaining to potential cancer diagnoses are regarded as “underused moments” for the provision of encouraging cancer risk-reducing behaviours.<sup>7</sup> When employing these moments to encourage behaviours that can reduce BC risk, the advice given should be based on a comprehensive understanding of the current evidence on modifiable lifestyle risk factors and how younger patients can most effectively influence their risk of disease.

This review presents current understanding of factors in young women associated with the development of primary BC, the direction of risk and the magnitude of effect. Whilst previous publications in this area have focussed on life-style associated risk factors, this article also includes a discussion of the categorisation of risk factors and the inclusion of reproductive and iatrogenic factors as well as those factors that can be most influenced by an individual’s behaviour. The interaction between modifiable and genetic factors is also considered.

## Methodology

An electronic literature review using PubMed (NLM) was performed. Search terms included “young” or “early onset”, and “breast cancer” and “modifiable risk”. All identified articles published in English language between 1960 and 2020 were assessed for suitability. Abstracts and reports from meetings not published in peer-reviewed journals were excluded. Additional references known to the authors or cited within reference lists of relevant papers were also investigated. Articles were excluded from this review if they contained solely post-menopausal data or if they contained data for risk factors that were non-modifiable such as age, sex and past history of breast cancer or proliferative breast disease, apart from genetic risk factors which were included. The last search was performed in October 2020.

## Results

### Defining “Young Women” in BC Research and Literature

The European consensus treatment guidelines for BC in young women define “young” as aged 40 years or below<sup>8</sup> partially based on the observation that women in this age group have poorer BC outcomes than older age groups.<sup>9</sup> However, most epidemiological studies of BC risk, including the World Cancer Research Fund (WCRF) continuous update project, stratify patients according to menopausal status (pre- or post-menopausal).<sup>10</sup> Although in some datasets this categorisation is based on biological indicators of ovarian function, age ranges of 0–50 or 0–55 years are frequently used as surrogate indicators of premenopausal status. It is therefore evident that premenopausal groups will contain data for “young women” (≤40 years), but will additionally include variable numbers of older women dependant on the data source. The biological differences in BC between age groups exist on a continuum so that a specific age threshold, such as below 40 years, alludes to trends in BC biology as opposed to definitive unique differences.<sup>11–13</sup>

### Categorising Risk Factors

Many factors have been implicated as factors that influence BC risk in a younger female population,<sup>14</sup> with variable effect sizes as well as variable degrees of modifiability.

Some factors associated with BC development are clearly “inherent” risk factors whereby an individual’s choices cannot influence the risk factor, such as the germline genome or pre-natal development. Other risk factors are potentially “modifiable” such as: physical activity, body weight/habitus, alcohol consumption, which are influenced by personal choice.<sup>15</sup>

Some factors discussed in this review are more nuanced. For example, increased parity appears to decrease risk of developing BC but problems such as infertility may confound one’s degree of personal choice over this factor. Iatrogenic risk factors are similarly more limited in terms of self-adjustment. These factors are referred to here as “less modifiable”.

### Features of Young Onset Breast Cancer

Women below the age of 40 with BC are more likely to die from the disease than older women.<sup>9,16,17</sup> This can be explained in part by the biological characteristics of tumours in this cohort.

BCs in young women have a higher frequency of more aggressive phenotypes than older women. Young patients are more likely to present with more advanced disease stage with larger tumour size, lymph node involvement, and less differentiated tumours.<sup>18–21</sup> Tumour biology also reflects more aggressive disease in younger women with increased frequency of oestrogen receptor (ER) negative and triple negative tumours,<sup>11</sup> and increased Ki-67 expression than in those over the age of 50 years.<sup>20,21</sup>

Women under 40 years at first breast cancer diagnosis have a higher frequency of a family history of BC and a higher chance of an underlying pathogenic mutation in a BC susceptibility gene than women diagnosed with breast cancer aged over 40 years.<sup>22</sup> *BRCA* gene mutations (either *BRCA1* or *BRCA2*) are found in approximately 12% of BC patients aged <40 years.<sup>4</sup> *TP53* germline mutations are found in 5% of diagnoses of BC aged ≤35 years<sup>23</sup> and *PALB2* mutations in approximately 1% in early-onset BC.<sup>24</sup> Mutation penetrance seems to be higher in younger than older women for some breast cancer susceptibility genes (CSGs); the relative risk of developing BC was 8–9 in *PALB2* mutation carriers below 40 years compared to 5–8 in women over 40 years.<sup>25</sup>

American studies have reported some notable racial variations in breast cancer age of onset, with black women experiencing significantly higher breast cancer incidence before the age of 40 years and lower incidence after age 50 compared with white women of the same ages.<sup>26</sup> Differences in breast cancer incidence rates between most racial/ethnic groups have been largely explained by risk factor distribution except in African Americans<sup>27</sup> where the higher incidence in the younger age group is not yet fully explained. Population-based studies in the UK have concluded that the younger age of Black Caribbean and Black African breast cancer patients in South East England reflects the younger age of these populations, rather than an increased risk of disease at younger ages<sup>28</sup>. Several non-age selected studies have reported increased incidence of adverse biological features in black women compared to white women. The POSH prospective study of 2915 breast cancer patients aged <41 years has confirmed this finding in young onset breast cancer with higher median tumour diameter and higher frequency of ER/PR/HER2-negative tumours in Blacks (26.1%) than Whites (18.6%,  $P=0.04$ ).<sup>29</sup>

## Modifiable Risk Factors

### Lifestyle Risk Factors

#### Physical Activity

In the past, there had been a general acceptance that physical activity has no effect on premenopausal BC risk following large-scale prospective cohort studies such as Rockhill et al (104 468 participants) which reported no association.<sup>30</sup> However, more recent data seem to contradict these findings. Since 2013, three independent meta-analyses<sup>31–33</sup> investigating the effect of physical activity on premenopausal BC have concurred that physical activity significantly reduces the risk of premenopausal BC development. Physical activity led to a 23% reduction in BC cases (RR 0.77; 95% CI 0.72–0.84) when comparing women in the highest versus the lowest categories of amounts and types of physical activity in a meta-analysis of 6 studies (2258 cases).<sup>31</sup> Hardefeldt et al's 2018 meta-analysis of 48 cohort studies found that physical activity significantly reduced overall risk (OR 0.79, 95% CI 0.73–0.87)<sup>32</sup> and finally Chen et al in 2019 reported an overall relative risk of 0.83 (95% CI 0.79–0.87) over 14,968 cases, of developing premenopausal BC associated with physical activity.<sup>33</sup> Therefore, it seems there is a recent body of evidence suggesting that physical activity may be key in reducing premenopausal BC risk.

#### Intensity and Duration of Exercise

Although evidence in premenopausal women is limited, it indicates a significant downward trend between increasing intensity (in metabolic equivalent task hours per week) and/or longer duration (hours per week) of physical activity in relation to BC risk.<sup>34</sup> For studies considering combined pre- and post-menopausal BC risk, for which there are significantly more data, the intensity of the exercise played a modest role in reducing risk. Engaging in “higher-intensity” activities (activity that causes you to sweat, ie, running and competitive sports) had a slightly greater risk reduction (OR 0.73; 95% CI 0.65–0.81;  $P<0.001$ ) than in those who did “low-intensity” activities (such as walking and gardening) (OR, 0.79; 95% CI, 0.72–0.86;  $P<0.001$ ).<sup>32</sup> A meta-analysis of 11 studies reporting amount of exercise and 11 studies reporting metabolic equivalent task hours per week (MET-h/week) demonstrated a significant dose-response relationship ( $p<0.0001$ ) between increasing intensity and/or duration of exercise per week and reductions in BC risk.<sup>35</sup> This method for reducing risk is especially important for a younger population, who tend to have an increased capacity for exercise; considering engaging in

higher intensity exercises may be an effective way of significantly reducing their BC risk.

### Type of Exercise

Chen et al's pooled analysis reported that overall relative risk reductions are associated with all types of physical activity (recreational, occupational and non-occupational) and the differences in risk between types of activity were modest. It remains unclear whether recreational physical activity specifically reduces risk in young women any more than occupational.<sup>36,37</sup>

### Adult Body Habitus/Body Mass Index

It seems that physiological differences between pre- and post-menopause alter the effect of body mass index (BMI) on risk of developing BC.<sup>38</sup> Younger adult women have a modest inverse correlation for BC risk with increasing BMI, according to many studies and meta-analyses (Table 1).<sup>39–46</sup> This is contrary to the positive correlation between BMI and BC risk in post-menopausal women.

This relationship is comprehensively summarised in Renehan et al's meta-analysis of 20 prospective cohort studies, which reported that for every 5kg/m<sup>2</sup> increase in BMI there was a significant decrease in relative risk of developing premenopausal BC (RR 0.92; 95%

CI 0.88–0.97), highlighting a dose-response effect of BMI on premenopausal BC.<sup>39</sup> The mechanism underpinning this effect is unclear and evidence limited, although it has been suggested that obesity causes ovarian suppression leading to decreasing levels of circulating oestradiol.<sup>47</sup>

BMI however is simply a marker of overall adiposity at a population level and does not inform us about the distribution of weight in the body in an individual. Waist-to-hip ratio (WHR) describes a pattern of adiposity (comparison of abdominal to gluteal fat), and increases in WHR are associated with increased risk of premenopausal BC. This was explored in a meta-analysis by Amadou et al<sup>42</sup> that used 9 case-control and 3 cohort studies to demonstrate a significant dose-response premenopausal BC relative risk increase of 1.08 (95% CI 1.01–1.16) per 0.1 unit increase in WHR, despite acknowledging that BMI was still associated with a significant dose-response decreased relative risk of premenopausal BC per 5kg/m<sup>2</sup> increase (RR 0.95; 95% CI 0.94–0.97).<sup>42</sup> This suggests that although increases in BMI (as a marker of general adiposity) decrease risk, central adiposity (deposited around the abdomen) is associated with increased risk of premenopausal BC.

Furthermore, although a higher BMI is protective in premenopausal women, the magnitude of risk reduction in premenopausal BC is less than the increased BC risk

**Table 1** Summary and Details of Meta-Analyses Investigating the Relationship Between BMI and Relative Risk (RR) of Developing Premenopausal BC

Author and Year	Study Type (Those Included)	Number of Cases	Menopausal Status	Age or Menopausal Status Based Studies?	BMI	RR (95% CI)
Ursin et al 1995 <sup>43</sup>	Meta-analysis: 4 cohort and 19 case-control studies	N/A	Premenopausal	Age-based: 6 studies	Per 8-unit increase	Cohort studies: 0.70 (0.54–0.91)
				Menopausal status based: 16 studies		Case-Control studies: 0.88 (0.76–1.02)
Van Den Brandt et al 2000 <sup>40</sup>	Meta-analysis: 5 prospective cohort studies	703	Premenopausal	Menopausal status	<21	1.0
					≥33	0.58 (0.34–1.00)
Bergström et al 2001 <sup>41</sup>	Meta-analysis: 2 cohort and 7 case-control studies	6533	Premenopausal	N/A	Per 1-unit increase	0.98 (0.97–0.99)
Renehan et al 2008 <sup>39</sup>	Meta-analysis: 20 studies	7930	Premenopausal	N/A	Per 5-unit increase	0.92 (0.88–0.97)
Amadou et al 2013 <sup>42</sup>	Meta-analysis: 11 cohort and 18 case-control studies	14,429	Premenopausal	Age and menopause status based	Per 5-unit increase	0.95 (0.91–0.98)

witnessed post-menopause.<sup>39</sup> Many studies agree that weight change during adulthood increases the risk of BC at an older age (post-menopausal).<sup>48–51</sup> Although true that a higher BMI can reduce BC risk in premenopausal women, the cumulative risk of developing BC across a person's lifetime will be increased in those with a high BMI.<sup>38</sup> Obesity is also associated with increased risk of other malignancies and other serious health issues. Therefore, gaining weight should not be recommended as a suitable method to reduce BC risk long term. Interestingly, in the Carolina Breast Study, higher adult body mass index was inversely associated with premenopausal breast cancer for Whites but not for Blacks;<sup>52</sup> Higher waist/hip ratio, adjusted for body mass index, increased risk for both black and white premenopausal women.<sup>53</sup>

### Alcohol

Swanson et al investigated the effect of alcohol consumption in young women (<45 years) in 1997, and found that those who drank more than 14 alcoholic drinks per week had the highest risk of developing BC (RR 1.73, 95% CI 1.2–2.6) compared with non-drinkers.<sup>54</sup>

Since then, many studies have investigated the effect of alcohol consumption on BC and most have found that alcohol increases risk of BC in young or premenopausal women.<sup>55–57</sup>

In their evaluation of evidence in 2018, the WCRF concluded that there was “strong probable” evidence that alcohol consumption increases the risk of premenopausal BC. A pooled multivariate analysis of 3730 cases of premenopausal women found that a 10g per day increment of alcohol consumption was associated with a BC RR of 1.03 (95% CI: 0.99–1.08), thus supporting the idea that a dose-response effect exists between alcohol and risk of premenopausal BC.<sup>58</sup> This supports the WCRF meta-analysis which found statistically significant evidence of dose-response relationship between alcohol and premenopausal BC risk, whereby an increase of 10g of ethanol per day led to a 5% increased risk of developing BC in premenopausal women.<sup>10</sup>

Type of alcohol beverage also appears to be significant when considering premenopausal BC risk. The WCRF's 2018 report concluded that consuming 10g of ethanol per day as beer had a RR of 1.32 (95% CI: 1.06–1.64) whereas from wine this was less (RR 1.17, 95% CI: 0.79–1.73) and from spirits the lowest (RR 1.10, 95% CI: 0.92–1.30).<sup>10</sup>

### Smoking

The impact of active smoking on BC risk in young women has been unclear since it was first discussed by MacMahon in 1982.<sup>59–61</sup> The Collaborative Group on Hormonal Factors in BC's meta-analysis showed that the effect of smoking on BC risk is confounded by its known association with alcohol.<sup>61,62</sup> However, most research concurs that if there is a risk associated with smoking, that it is more influential in premenopausal (than post-menopausal) BC risk.<sup>63–65</sup> Women who commence smoking at a young age seem to have a higher lifetime BC risk than those who take up smoking in later life. A cohort study of 1815 women with invasive BC found that the hazard ratio for all “ever” smokers (compared to never smokers) was 1.14 (95% CI 1.03–1.25;  $p=0.010$ ) rising to 1.24 (95% CI 1.08–1.43;  $p=0.002$ ) for starting smoking at ages <17 years.<sup>66</sup>

Interestingly, passive smoking may be a greater risk factor for BC than active smoking. It has been postulated that active smoking is associated with an anti-oestrogenic effect which may to some extent counteract exposure to smoking-related carcinogens. Passive smoking does not “benefit” from the anti-oestrogenic effect but results in continued exposure to carcinogenic compounds (ie, N-nitrosamines, benzenes, carbon monoxide and carbon dioxide) which persist in side stream smoke and therefore, a relatively increased risk of breast oncogenesis.<sup>64,67,68</sup> A meta-analysis including 14 studies of smoking and premenopausal BC risk found that passive smoking was associated with an increased risk (pooled RR 1.68, 95% CI 1.88–2.12) increasing to a pooled summary risk estimate of 2.19 (95% CI 1.68–2.84) when the analysis was limited to the 5 studies with more complete exposure data.<sup>63</sup>

Individual studies place emphasis on genetic susceptibility and how this, compounded with exposure to secondary smoke, greatly increases BC risk.<sup>64,69</sup> For example, one study found that passive smoke exposure increased premenopausal BC risk in PARP1 or ESR1 genetically susceptible individuals (OR 1.54 95% CI 1.14–2.07).<sup>69</sup>

### Other Lifestyle Factors

#### Night Shift Work

Long-term rotating night shift work in young adulthood is particularly associated with increased risk of ever developing BC according to an analysis of two large-scale prospective cohort studies ( $n=9541$  total invasive BCs) in the United States: The Nurses' Health study (NHS) and Nurses' Health study II (NHS-II).<sup>70</sup> This

analysis found that in the NHS, women who had done 30 years or more of shift work did not have a higher risk of breast cancer (HR 0.95; 95% CI 0.77–1.17) compared with those who had never done shift work. However, participants of the NHS-II, who were a younger cohort (by approximately 20 years) than those in NHS had a significantly higher risk of breast cancer with 20 years or more of shift work (HR=2.15, 95% CI 1.23–3.73), and a significantly higher risk for women with 20 years or more of cumulative shift work (HR=1.40; 95% CI 1.00–1.97) compared to those who had never done shift work.<sup>70</sup> This conclusion is supported by a Spanish case-control study (OR 1.08; 95% CI 0.98–1.79)<sup>71</sup> which found that night shift work was a higher risk factor in premenopausal than post-menopausal BC.

Sherhammer et al found that there was a non-significant increase in premenopausal BC relative risk with number of years on rotating night shift work, and that the risk of developing premenopausal breast cancer appeared to increase with increasing years on a rotating night shift (“Never” worked a night shift age adjusted RR: 1.0; “1–14 years” RR 1.23, 95% CI 0.98–1.56); “≥15 years” RR: 1.30, 95% CI 0.75–2.26).<sup>72</sup>

A recent pooled analysis by Coridina-Duverger et al<sup>73</sup> using studies from 5 different “western” countries: Australia, Canada, France, Germany and Spain found that there was a pooled odds ratio of developing premenopausal BC of 1.26 (95% CI 1.06–1.51) associated with having “ever” worked a night shift for 3 or more hours between midnight and 5am. This risk increased to 2.55 (95% CI 1.03–6.30) for those who had been working the most night shifts per week (3 or more per week) and for a longer period of time (>10 years).

Working at night causes disruptions in circadian rhythm, whereby the “light-at-night” causes a suppression of pineal gland production of the hormone melatonin.<sup>74</sup> Pre-clinical trials suggest that melatonin exerts tumour-suppressive effects through a variety of mechanisms, including modulation of the oestrogen pathway, producing an anti-oestrogenic effect. Therefore, it is hypothesised that the absence of melatonin can lead to breast tumour growth.<sup>75</sup>

### Socioeconomic Status (SES)

Globally in 2020, the highest incidence rates for premenopausal BC occur in high human development index (HDI) regions (such as Western Europe, Australia and New Zealand and North America), however low human

development index regions (such as North and West Africa) had higher new cases and mortality with premenopausal BC in proportion to those of higher income.<sup>76</sup>

There is a lack of data for the impact of SES within a young US population. However, Akinyemiju et al<sup>77</sup> looked at SES across different ethnicities in a US population and found that combined early and late BC risk increased with increasing socioeconomic status. This shows concordance with current understanding of this relationship whereby women of higher socioeconomic status are at the highest risk of developing BC but have better survival outcomes from their diagnoses than lower-income areas in the US.<sup>78</sup>

An analysis of data from the Wisconsin longitudinal study (4275 women) found that having a higher socioeconomic status (SES) in early life/childhood and being born of a mother of a higher educational level increased BC incidence.<sup>79</sup> The underlying reasons may be that higher SES individuals tend to be older at the age of their first pregnancy and have decreased parity compared with lower SES.<sup>79,80</sup>

### Lifestyle Factors Conclusions

The evidence suggests that physical activity reduces the risk of premenopausal and early onset breast cancer with a dose-dependent effect and for all types of activity and so should be recommended. In contrast, although there is a slight risk reduction seen for premenopausal breast cancer with increased BMI this is offset both by the larger increased risk for post-menopausal breast cancer and the more general and cardiovascular risks of obesity and so maintaining a healthy weight, BMI and body composition should be recommended. Alcohol is perhaps one of the more easily modifiable risk factors and there is a dose-dependent relationship with breast cancer risk so should be reduced wherever possible. The effects of smoking may be confounded by alcohol intake but should be avoided regardless due to the overall harm to health beyond that of breast cancer alone. Socioeconomic status and shift working patterns are less easily modifiable and are perhaps more easily addressed at a public health and population rather than individual level.

### Reproductive Risk Factors

Within high-income countries, there has been a shift in reproductive behaviours, favouring fewer children per household and at a later stage in a woman’s reproductive timeframe. Simultaneously, there has been an increased

uptake in the use of exogenous hormonal medications, in the form of the oral contraceptive pill (OCP), intrauterine hormonal devices and menopausal hormone therapy (MHT), as cultural shifts have occurred within society.<sup>81</sup> Epidemiological evidence associates both exogenous and endogenous hormone exposure with an increased risk of BC<sup>82</sup> with exogenous hormone use being amenable to risk modification. There are two types of oestrogen (conjugated equine oestrogen and oestradiol) and four types of progestogen (norethisterone acetate, levonorgestrel, medroxyprogesterone, and dydrogesterone) commonly prescribed in the UK.<sup>83</sup>

### Hormonal Contraceptives

In 2018, the OCP was the main method for contraception for 28% of women in the UK and was the most common method used by women aged between 15 and 49 years.<sup>84</sup>

In 1996, a large collaborative dataset confirmed the association of an increased risk of BC with OCP use. This analysis compared OCP use in 53,297 women with BC and 100,239 women without a BC diagnosis and concluded an overall relative risk (RR) of BC in OCP users of 1.24 (95% CI 1.15–1.33).<sup>85</sup> On stopping the OCP the modest increased risk disappeared after 10 years (RR 1.01 95% CI 0.96–1.05). In real terms, this equates to one additional BC case with OCP use among 20,000 women aged 20–25 years using this form of contraception.<sup>82</sup> For women with a higher background risk, such as strong family history or high risk genetic mutation carriers, the data are limited but suggest the same effect in BC risk as for the overall population.<sup>82</sup> A more recent Danish paper has shown that the duration of contraceptive pill use to be important, with 13 years use associated with the highest increase of relative risk at 18% compared to a 5% RR increase for five years use.<sup>86</sup> Mørch et al calculated an overall BC risk with users of any hormonal contraceptive to be one extra BC case for every 7690 women using hormonal contraception for 1 year. Long-term hormonal contraceptive use has not been found to be associated with increased total cancer risk however.<sup>87</sup> As the overall population risk for BC in women in their 20s is low, the absolute risk for BC with OCP use is therefore small (1:20,000). In an older cohort of women (over 35 years old), with increased overall risk including family history, the additional increased RR with age with the OCP use is an important consideration. Long-term follow-up data on women using the OCP have shown a considerable protection against cancer of the ovary (RR= 0.67), endometrium (RR= 0.66), or colorectum (RR= 0.81).<sup>88</sup> Physicians need to establish a risk-benefit

ratio on an individual basis to enable a joint decision between the physician and patient on the use of hormonal contraception. For example, patients with *BRCA1* mutations will be at potentially increased risk of BC with OCP use, versus a protective effect for ovarian cancer risk should they not be planning a risk-reducing oophorectomy.<sup>89</sup>

An increased risk has also been noted with the progestin-only intrauterine system (levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena<sup>®</sup>)) compared to women who had not used hormonal contraceptives (RR 1.21; 95% CI 1.11 to 1.33).<sup>86</sup>

The use of a LNG-IUS is often informed by the need to control heavy menstrual bleeding and avoidance of gynaecological procedures. A recent systematic review and meta-analysis on LNG-IUS users concluded an overall increased risk of BC for all users (odds ratio OR = 1.16; 95% CI 1.06–1.28) with an increased risk in women over 50 years (OR = 1.52 (95% CI 1.34–1.72)).<sup>90</sup> A risk–benefit discussion between gynaecologist and patient, taking into account personal BC risk factors, is recommended prior to commencement of this long-term hormonal treatment.

### Menopausal Hormonal Therapy

Premature menopause before the age of 40 (in the absence of treatment for cancer) is rare affecting 1% of women.<sup>91</sup> However, the adverse impact of menopausal symptoms on quality of life in women with premature menopause is well documented and exogenous hormonal replacement therapy (HRT; or menopausal hormonal therapy MHT) is frequently recommended for their relief and also sometimes for bone protection purposes. There are predominately two main forms of preparations: unopposed oestrogen therapy and combined oestrogen and progestin preparations.<sup>82</sup>

A large meta-analysis of worldwide epidemiological evidence for type and timing of MHT and BC risk was published in the *Lancet* in 2019.<sup>92</sup> This study did include women aged 30–39 but there were insufficient data to analyse the impact on breast cancer risk associated with use of MHT for <5 years in this age group. Current use of MHT for 5–15 years starting between ages of 30–39 was not overall found to be associated with a statistically significant increased risk (RR 1.07; 95% CI 0.88–1.31) associated with a RR of 1.07 (95% CI 0.88–1.31).

The UK National Institute for health and Care Excellence (NICE) guidelines for patients with a -familial BC risk recommend tailoring of MHT to individual needs and seeking alternatives to MHT where possible. MHT should generally be prescribed at the

lowest dose required to control symptoms and for as short a duration as possible.<sup>89</sup> However, when women with no personal history of breast cancer have either a *BRCA1* or *BRCA2* mutation or a family history of breast cancer and they have had a bilateral salpingo-oophorectomy before their natural menopause, they can be offered either combined HRT if their uterus remains or oestrogen-only HRT if their uterus has been removed, up until the time they would have expected natural menopause (average age for natural menopause is 51–52 years).<sup>89</sup>

### Fertility Enhancement and Preservation Techniques

Women who decide to have children later in life may undergo fertility techniques for oocyte harvesting, oocyte cryopreservation and embryo transfer techniques and fertilisation (In vitro fertilisation (IVF)). Follicle-stimulating hormone (FSH) injections are often used daily for 2 weeks to stimulate follicle development and assist harvesting. No association has been reported between use of fertility preservation techniques and BC development,<sup>82</sup> including for *BRCA 1/2* mutation carriers. IVF exposure was not associated with risk of BC (HR: 0.79, 95% CI: 0.46–1.36).<sup>93</sup> A recent systematic review has highlighted however there is limited evidence on the association between IVF and premenopausal breast cancer risk.<sup>94</sup>

### Pregnancy and Parity

The age at which a woman gives birth to a child has been shown to influence her BC risk.<sup>81</sup> Arguably, timing of pregnancy and child-bearing is not always planned, however a woman with an increased BC risk may wish to actively start a family earlier to reduce her BC risk. The age at first pregnancy is especially important, with parity under 20 years of age associated with the longest term risk reduction of 50% compared to nulliparous women.<sup>95</sup> Having a child over 35 years of age conferred an increased BC risk compared to a nulliparous woman.<sup>96</sup> Recent data suggest that the age of first pregnancy and parity affects the risk of specific BC subtype development, with young age of first pregnancy and parity being associated with a reduction in luminal oestrogen receptor positive BCs but not other subtypes.<sup>97</sup>

Post-partum there is a transient observed increase in BC risk which is attributed to the post-partum involution process within the breast.<sup>81</sup> It is hypothesised that the breast remodelling following lactational changes takes up to ten years on average and the increased risk may be due to immune micro-environment changes.<sup>81</sup> The reduction in BC risk following

this period may be due to a reduction in ER sensitive epithelial cells within the breast.<sup>98</sup> Compared to nulliparous women, parous women have an increased BC risk peaking 5 years after birth before decreasing up to 34 years later (HR, 1.80 [95% CI, 1.63 to 1.99]) and 0.77 (CI, 0.67 to 0.88, respectively).<sup>99</sup>

Data from the 1993–2001 Carolina Breast Cancer Study which included 1505 African-American and 1809 White women identified some important racial differences in breast cancer risk factors amongst younger women (aged 20–49). Multiparity was associated with increased risk of breast cancer among younger African-American women (for three or four pregnancies: adjusted odds ratio (OR) = 1.5, 95% confidence interval (CI): 0.9, 2.6; for five or more pregnancies: OR = 1.4, 95% CI: 0.6, 3.1) but not among younger White women (for three or four pregnancies: OR = 0.7, 95% CI: 0.4, 1.2; for five or more pregnancies: OR = 0.8, 95% CI: 0.2, 3.0). The relationship with age at first full-term pregnancy and nulliparity also varied by race.<sup>100</sup> Thus, the higher incidence of breast cancer among younger African-American women may result from both higher prevalence of risk factors and higher relative risks associated with these.

### Breastfeeding

Breastfeeding has been shown to reduce a woman's risk of BC.<sup>101</sup> The mechanism of risk reduction is not clear; however, for every 12 months of breast feeding, the RR reduction is 4% for all women with an increased RR reduction of 5.1% for premenopausal BC.<sup>81,102</sup>

Interestingly, the protective effect of breast feeding is not limited to only hormone receptor positive breast cancer subtypes.<sup>103</sup> A reduction in risk has also been demonstrated in hormone receptor negative breast cancers which are more common in younger women.<sup>104</sup>

The World Health Organisation recommends at least six months of breast feeding post-partum prior to weaning for a protective effect.<sup>105</sup> Young mothers should be supported to breastfeed to reduce their BC risk in addition to promoted benefits to the developing baby.

### Risk-Reducing Medications

Anti-oestrogen medications may be offered in specialist clinics to women with high and moderate personal risk for BC.<sup>106</sup> These medications are referred to as “chemoprevention” however risk-reducing medication is a more favourable term to encourage uptake.<sup>81</sup>



In premenopausal women, use of tamoxifen for 5 years reduced BC risk by 33% and the reduction persisted for at least 15 years after cessation of the anti-hormonal medication.<sup>107,108</sup> Of note, there was no benefit shown for overall BC mortality with this treatment. They may be a useful option for women with high to moderate risk of BC who wish to reduce their risk as an alternative or bridge to risk-reducing surgery.<sup>106</sup> Caveats to the use of tamoxifen are an increased risk of venous thromboembolism and endometrial cancer (risk 4:1000). A short trial of tamoxifen for six to eight weeks may feel more acceptable to a patient prior to a five-year course to test for medication induced side effects.<sup>81</sup> Although raloxifene and aromatase inhibitors have been shown to reduce breast cancer occurrence in high risk post-menopausal women, these drugs are not recommended in premenopausal women.<sup>89</sup> Non-hormonal forms of chemoprophylaxis for breast cancer remain under investigation. Several meta-analyses of observational studies have reported reduced risk of breast cancer in aspirin users compared to non-users.<sup>109,110</sup> However, in their subgroup analysis, Cao et al found a significant risk reduction of breast cancer associated with aspirin use in post-menopausal women (RR=0.89, 95% CI: 0.83–0.96,  $P=0.002$ ), but not in premenopausal women (RR=0.88, 95% CI: 0.72–1.08,  $P=0.223$ ).<sup>110</sup>

#### Reproductive and Hormonal Factors Conclusions

In younger women less than the age of 35 the absolute increased breast cancer risk with the combined oral contraceptive is very small and so this can be prescribed with appropriate information. Between the age of 35 and 50 women with a breast cancer family history should be aware that the increased breast cancer risk increases with age as their absolute familial breast cancer risk increases and this should be weighed within the overall risks and benefits of the combined oral contraceptive. For those with *BRCA1* or *BRCA2* gene alterations considering the combined oral contraceptive the situation is more complex and specialist genetic service input may be beneficial to judge the competing impacts of increased breast cancer risk against reduced ovarian cancer risk within the specific circumstances of the individual.<sup>111</sup> For those with an early menopause no increased risk is seen with HRT up to the natural age of menopause for a general population, but in those with increased familial risk more specialist input may again be helpful.

## Iatrogenic Risk Factors

### Breast Implants

Worldwide it is estimated that over 1.8 million breast augmentation procedures are performed annually, of which 2.8% are in those aged 18 years or younger, 53.9% in those aged 19–34 and 35.0% in those aged 35–50. The UK independent review group on Silicone Gel Breast Implants concluded that BC incidence is not raised in women with breast implants,<sup>112</sup> however, in those with cosmetic breast augmentation breast cancer diagnosis appears to occur at a later stage and possibly impacts negatively on survival.<sup>113</sup> More recently an association has been identified between silicone breast implants and a form of non-Hodgkin lymphoma known as Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). This typically occurs 7–10 years following implantation,<sup>114</sup> and so given the demographics of cosmetic breast augmentation surgery will be relevant to younger women considering such surgery. The MHRA estimates that the incidence of the BIA-ALCL is 1 per 20,000 implants sold,<sup>115</sup> and since cosmetic augmentation is usually a bilateral procedure, the rate may be 1 per 10,000 in women undergoing cosmetic implant breast augmentation.

### Treatment of Hodgkin Lymphoma (HL)

It has been recognised since the 1980s that treatment for Hodgkin's Lymphoma (HL) is associated with a subsequent increased risk of BC amongst other secondary malignancies, with an increasing risk over time for over three decades after HL diagnosis. A recent study of 200 945 survivors of teenage and young adult cancer survivors reporting cumulative risk of BC of 0.3%, 1.3%, 3.8%, 6.7%, 10.8% and 14.4% at 10, 15, 20, 25, 30 and 35 years after HL diagnosis.<sup>116</sup> Risk of BC in HL survivors is closely associated with use of mantle irradiation with both total dose and field size/site of irradiation influencing risk levels.<sup>117</sup> A significantly lower risk of BC has been reported among patients who received supradiaphragmatic field radiotherapy not including the axilla than among those who received complete mantle-field radiotherapy (HR, 0.37; 95% CI 0.19 to 0.72).<sup>118</sup> Recognition of these risk factors led to adoption of potentially less toxic treatment regimes in the late 1980s incorporating smaller and less intense radiation fields. However, recent cohort studies comparing second malignancy rates in patients treated for HL during different time periods have not indicated the anticipated fall in treatment-related BC rates with newer treatment regimens.<sup>118,119</sup> It is postulated that this is due to the simultaneous adoption of less toxic

chemotherapy regimens with a lower incidence of premature menopause with associated reduction in oestrogen exposure.

Age at time of HL diagnosis is an important modifier of risk. Studies of childhood cancer survivors however indicate that radiation treatment at age 10–16 years carries more risk than treatment at age <10 (RR 1.9).<sup>117</sup> In the teenage and young adult (TYA) population RR is significantly higher for those treated for HL at age <19 than those treated at 20–29 years with no increased BC risk for HL patients diagnosed at ≥30 years.<sup>120</sup>

For women who received radiotherapy for HL between the ages of 10–29, current UK guidelines recommend that breast screening in the form of an annual magnetic resonance imaging (MRI) scan should start 8 years after radiotherapy to breast tissue or at age 25 or 30 (whichever occurs later). Women treated between the ages of 30–39 should commence annual breast MRIs at age 30.<sup>121</sup>

## Interactions Between Genetic and Modifiable Risk Factors for Young Breast Cancer

Female HL patients with a family history of BC are significantly more likely to develop BC, compared to HL patients with no history of BC among relatives.<sup>119,122</sup> However, there is currently no evidence that there is a role for mutations in the known high penetrance BC susceptibility genes *TP53*, *BRCA1*, *BRCA2*, and *ATM* as a cause of subsequent cancer risk in HL survivors.<sup>123</sup>

Some studies report that there are important interactions between an individual's genetics (their background risk) with lifestyle risk factors that can alter the effect size or direction of risk. Niehoff et al demonstrated that recreational physical activity does not reduce risk in premenopausal women with a family history of BC,<sup>124</sup> contrary to the effect seen in young women without familial history.

Tryggvadottir et al<sup>125</sup> investigated the changes in risk of developing any BC associated with *BRCA2* mutations in an Icelandic population, reporting that there was a four-fold increase of incidence of BC in *BRCA2* mutation carriers in 2000 (compared to 1920), ultimately concluding that *BRCA2* mutation penetrance has increased with time. This work concluded that this increase in penetrance was proportional to increases in the Icelandic population of modifiable BC risk factors which have increased over time. Additionally, a case-control study by Jernström et al showed that young women (below age 40 years)

who carried *BRCA1* and *BRCA2* mutations would be at higher risk of developing BC with increasing number of pregnancies. Therefore, the direction of a partially modifiable risk factor such as parity is dependent on whether they have wild type or mutant *BRCA1* and 2 genes.<sup>126</sup> Tobacco smoking in *BRCA1* and 2 mutation carriers increases risk of developing BC by 17% compared to mutant non-smokers, and women with the highest pack years (4.3–9.8) having a 33% increase of BC (HR=1.33 9% CI 1.02–1.75).<sup>127</sup> More research is needed to investigate the interactions between genetic effects and other factors.

Counselling and health education for premenopausal women with a family history of BC is complex. Communicating DNA-based disease risk estimates for conditions where risk could be reduced by behaviour change produced no significant effects on smoking, diet, physical activity or alcohol use behaviours.<sup>128</sup> An interview study of premenopausal women with a family history of BC who were overweight/obese found that they had feelings of guilt and anxiety when unable to lose weight. Therefore, credible rationales for weight loss that address these feelings of anxiety and doubt are required to reduce this significant risk factor in this high risk population, as well as appropriate support.<sup>129</sup> In a feasibility study of 79 overweight premenopausal women at increased risk of breast cancer, 55% of those enrolled in a 12-month diet and exercise weight loss programme (n = 40) achieved target weight loss of 5% baseline weight, compared to 15% of those receiving usual care in the form of a healthy lifestyle advice leaflet.<sup>130</sup>

## Conclusions

BC is the most common cancer diagnosis in women aged under 40 and associated with poorer survival outcomes than in older women. As incidence of young onset BC increases globally there is an urgent need to address risk factors that are modifiable by individual behaviour change.

Overall risk is however determined by both modifiable and non-modifiable risk factors and the most significant non-modifiable risk factor is often familial risk. Health care professionals should therefore assess BC inherent and familial risk through a careful medical and family history and aim to discuss modifiable factors in relation to this background risk. Modifiable risk factors (Table 2) including physical activity and alcohol habits should be considered whenever presented with a “teachable moment” applicable to breast health. Discussions regarding personal risks and benefits

**Table 2** Summary of the Key Evidence Regarding Specific Risk Factors in Relation to the Risk of Developing Breast Cancer at a Premenopausal Age/Stage

Risk Factor	Author and Year	Type of Study	Effect on Risk of Premenopausal Breast Cancer	Comparator	Magnitude of Risk (95% CI)
<b>Physical Activity</b>					
	Wu et al 2013 <sup>31</sup>	Meta-analysis	Reduced	“Highest” vs. “lowest” categories of amount of physical activity	RR 0.77 (0.72–0.84)
	Hardefeldt et al 2018 <sup>32</sup>	Meta-analysis	Reduced	Effect of “any” exercise intervention vs. “none”	OR 0.79 (0.73–0.87)
	Chen et al 2019 <sup>33</sup>	Meta-analysis	Reduced	Effect of “any” exercise intervention vs. “none”	RR 0.83 (0.79–0.87)
<b>BMI</b>					
	Ursin et al 1995 <sup>43</sup>	Meta-analysis	Reduced	Per 8- unit increase in BMI (kg/m <sup>2</sup> )	Cohort Studies: RR 0.70 (0.54–0.91) Case-control studies: RR 0.88 (0.76–1.02)
	Renehan et al 2008 <sup>39</sup>	Meta-analysis	Reduced	Per 5-unit increase in BMI (kg/m <sup>2</sup> )	RR 0.92 (95% CI 0.88–0.97)
	Amadou et al 2013 <sup>42</sup>	Meta-analysis	Reduced	Per 5- unit increase in BMI (kg/m <sup>2</sup> )	RR 0.95 (95% CI 0.91–0.98)
<b>Alcohol</b>					
	Jung et al 2016 <sup>58</sup>	Meta-analysis	Increased	Per 10g ethanol per day increase	RR 1.03 (95% CI 0.99–1.08)
	WCRF Report, 2018 <sup>10</sup>	Meta-analysis	Increased	Per 10g ethanol per day increase	RR 1.05 (95% CI 1.02–1.08)
<b>Smoking</b>					
Active smoking	Jones et al 2017 <sup>66</sup>	Cohort study (1815 participants)	Increased	“Ever” smokers vs. “Never” smokers	HR 1.14 (95% CI 1.03–1.25)
	Macau et al 2015 <sup>68</sup>	Meta-analysis	Increased	“Ever” smokers vs “Never” smokers	6 prospective studies: RR 1.11 (1.00–1.25)
Passive Smoking	Johnson 2005 <sup>63</sup>	Meta-analysis	Increased	Exposure to second hand smoke in women who had never smoked vs. no adequate exposure	All 14 studies: Pooled RR 1.68 (1.33–2.12) 5 studies corrected for more comprehensive passive smoke exposure assessment: RR 2.19 (1.68–2.84)
	Macau et al 2015 <sup>68</sup>	Meta-analysis	Increased	“Ever” exposure to passive smoking compared with “never”	5 prospective studies: RR 1.16 (0.62–2.16)

(Continued)

Table 2 (Continued).

Risk Factor	Author and Year	Type of Study	Effect on Risk of Premenopausal Breast Cancer	Comparator	Magnitude of Risk (95% CI)
Night Shift Work					
	Wegrzyn et al 2016 <sup>70</sup>	Analysis of data from 2 prospective cohort studies: Nurses' Health Study and Nurses' Health Study II	NHS: No effect NHS-II: Increased	NHS: ≥30 years of shift work compared to "never" NHS-II: ≥20 years of shift work compared to "never"	NHS: HR 0.95 (0.77–1.17) NHS-II: HR 2.15 (1.23–3.73)
	Cordina-Duverger et al 2018 <sup>73</sup>	Meta-analysis	Increased	"Ever" compared to "Never" having worked a night shift for 3 or more hours between midnight and 5am	Pooled OR 1.26 (1.06–1.51)
Hormonal Contraception					
	van den Brandt et al 1996 <sup>85</sup>	Meta-analysis	Increased	In "Ever" users compared to "never" users of the COCP	RR 1.07 (1.04–1.10)
			Increasing	"Current use" or "Time since last use" compared to "never" users of the COCP	Current User: RR 1.24 (1.15–1.33), 1–4y Since last use: RR 1.16 (1.08–1.23), 5–9y since last use: RR 1.07 (1.02–1.13)
	Mørch et al 2017 <sup>86</sup>	Prospective Cohort study (1.8 million participants)	Increased	"Ever" use of an LNG-IUS (Mirena®) compared to "never" used hormonal contraceptive	RR 1.21 (1.11–1.33)
Younger age at first pregnancy					
	MacMahon et al 1970 <sup>95</sup>	Case-Control (4323 cases, 12,699 controls)	Reduced	Comparing "age at first birth" sub-groups to "nulliparous"	Nulliparous: RR 1.00, ≤20y: RR 0.50, 20–24y: RR 0.60, 25–29y: RR 0.78, 30–34y: RR 0.94, ≥35y: RR 1.22
Breastfeeding					
	Collaborative Group on Hormonal Factors in Breast Cancer, 2002 <sup>102</sup>	Meta-analysis	Reduced	Per 12 months of breastfeeding	All breast cancer: 4.3% reduction in RR Premenopausal breast cancer: 5.1% reduction in RR

**Abbreviations:** RR, relative risk; OR, overall risk; HR, hazard ratio.

should also accompany conversations regarding reproductive health and hormonal preparations, and take into consideration other modifiable risks and the background individual non-modifiable and iatrogenic BC risk factors. Increasing understanding of the interactions between genomic and modifiable factors will be vital in providing individualised advice

to young women who wish to minimise their personal BC risk.

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