Parabens and breast cancer

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Peer reviewed by two members of Breast Cancer UK independent Science Panel

1. Summary

Parabens are Endocrine Disrupting Chemicals (EDCs) used as preservatives to stop the growth of microorganisms in cosmetics, personal care products and some processed foods. They can be ingested or absorbed through the skin and have been found in many body fluids and tissues, including in the breast. In laboratory studies, parabens were found to interfere with the female hormone oestrogen and increase the risk of mammary tumours in animals. However, only a limited number of human studies have been carried out and these are inconclusive regarding the possible link to breast cancer. Nonetheless, exposure to parabens should be reduced by seeking paraben-free cosmetics and personal care products. Regulations should also be tightened, especially for parabens officially recognised to be EDCs. Breast Cancer UK is calling for the phasing out and removal of EDCs from non-essential products.

2. Parabens and their uses

Para-hydroxybenzoic acid and parabens are synthetic chemicals used as preservatives in cosmetics and food to stop the growth of microorganisms [1]. Parabens are also referred to as esters of para-hydroxybenzoic acid and can be produced naturally by plants and bacteria [1].

The most common use for parabens is as preservatives in personal care products, such as shampoos, conditioners, deodorants, creams, lotions and mouthwash [2,3]. Within these products, the most used paraben is methylparaben, whilst butylparaben is the least common [4].

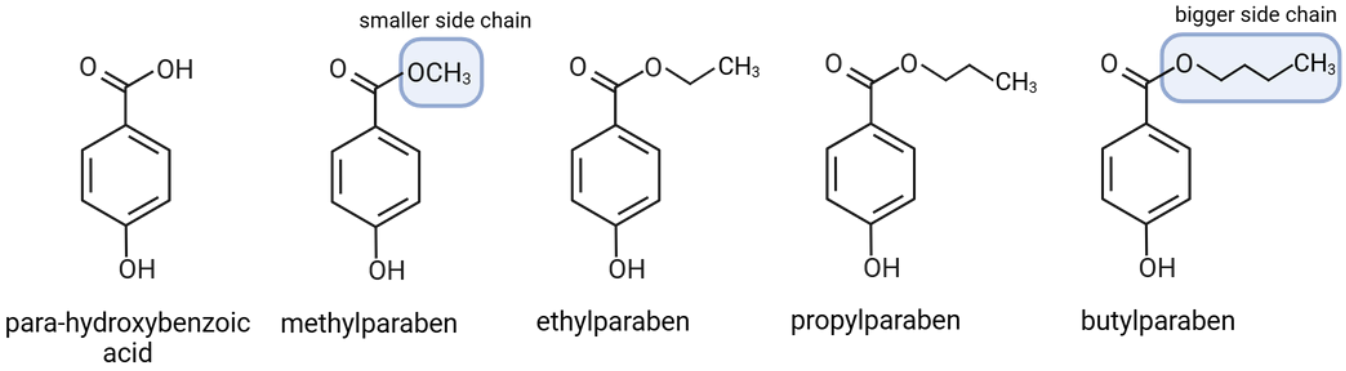

Figure 1. Chemical structure of the parabens. Created with BioRender.com

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These chemicals have also been found in menstrual and female hygiene products [5] as well as pharmaceuticals and medicines [2]. Although not common in the UK, methylparaben, ethylparaben and their salts can also be used as preservatives in food, mainly in processed and precooked meat, cereal and potato-based snacks, coated nuts, and confectionery [6]. In these products, parabens are listed on the ingredients label as the following E numbers: E214, E215, E218 and E219 [7].

3. Exposure and metabolism

The use of cosmetics and personal care products is the main source of exposure to parabens, which is generally higher in women compared to men and children [8,9]. This group of chemicals can be easily absorbed through the skin and leave-on products, like lotions and make-up, can provide continuous and prolonged exposure [2].

When parabens are ingested, they are rapidly metabolised (broken down) to para-hydroxybenzoic acid and this is eliminated in the urine within 8-12 hours [1,10]. However, when they are absorbed through the skin, they might not be metabolised and can be eliminated in the urine in their original form [11]. For this reason, paraben levels in the urine are linked to the use of cosmetics [10,12], with methyl-paraben usually found in higher concentrations compared to butyl-paraben [1].

Parabens have also been measured in blood, amniotic fluid, cord blood, breast milk and placental and breast tissues [5,13–19]. Studies have shown that exposure to parabens can be effectively reduced by swapping cosmetics and personal care products with EDC-free versions [9,20,21].

However, this may not be sufficient to protect health as parabens have also been found in the environment [5], drinking water [22], river water [23], groundwater [24], soil and sediments [25], aquatic organisms [26], as well as in house dust, and indoor and outdoor urban air [27–29].

4. Parabens in breast tissue

Although parabens may be metabolised shortly after entering the human body, unmetabolised parabens have also been measured in the body and breast tissues [14,30–32]. The analysis of breast tumours found at least one paraben in all of the samples and methylparaben was present in the highest amounts, which is consistent with its widespread use in personal care products [30,31]. Parabens were also measured in 99% of non-cancerous breast tissue samples obtained from patients with breast cancer [14]. Furthermore, when comparing the concentration of parabens in breast cancer tissue with benign breast tumours, the cancerous tissue was found to have higher levels of parabens [32]. This suggests that these chemicals may preferentially accumulate in cancerous tissue, where they could display oestrogenic activity (see Section 5.1) [32].

5. Parabens and breast cancer

Growing evidence shows that parabens are Endocrine Disrupting Chemicals (EDCs) that may interfere with our hormone system, in particular with the female hormone oestrogen [33]. This hormone is responsible for many important biological events that are initiated by binding to oestrogen receptors (ER) in cells [34]. However, high levels of oestrogen can also encourage cells to divide rapidly (a process known as cell proliferation) which can increase the possibility of mutations, including those that lead to breast cancer [35]. Therefore, high levels of oestrogen can increase breast cancer risk [36] and EDCs with oestrogenic properties may play a role in breast cancer [37].

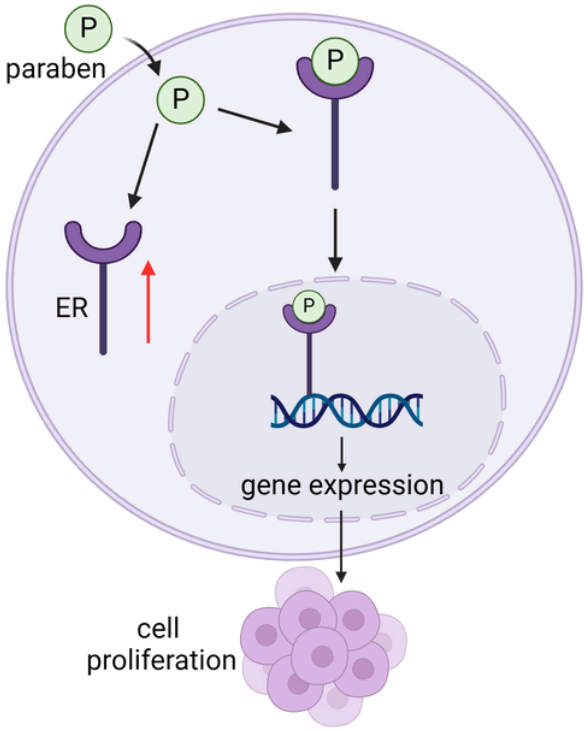

Figure 2. Parabens (P) can increase the production of oestrogen receptors (ERs) or bind to the ER mimicking oestrogen. After binding to the ER, they can regulate gene expression and increase cell proliferation. Created with BioRender.com

5.1 Cell studies

Laboratory studies have shown that parabens and para-hydroxybenzoic acid have weak oestrogenic activity in both normal and breast cancer cells [4,33,38–45]. By mimicking oestrogen, parabens can directly bind to ERs [1,2,46–49] and regulate gene expression [1,2,49,50], metabolism [51] and increase cell proliferation [1,33,46–48,51].

Their ability to bind to the ER is dependent on their chemical structure and parabens with bigger side chains (Figure 1) bind more strongly and therefore have higher oestrogenic activity [1,4,45,46,49,50]. The order of oestrogenicity of these chemicals, from higher to lower, is as follows: butylparaben > propylparaben > ethylparaben > methylparaben > para-hydroxybenzoic acid [33,52]. However, even the most potent paraben is much weaker than oestrogen, therefore the concentration of parabens needed to have an oestrogenic effect is much higher (at least 100,000 times higher) than that of natural oestrogen [1,33,46].

Nonetheless, studies have shown that parabens may be harmful at concentrations relevant to human exposure [39,48,51,53]. For example, butylparaben was measured in the blood at concentrations that, after accounting for its weaker oestrogenic activity, are similar to the levels of oestradiol (a potent form of oestrogen) in the breast (Figure 3) [11,54]. Furthermore, when

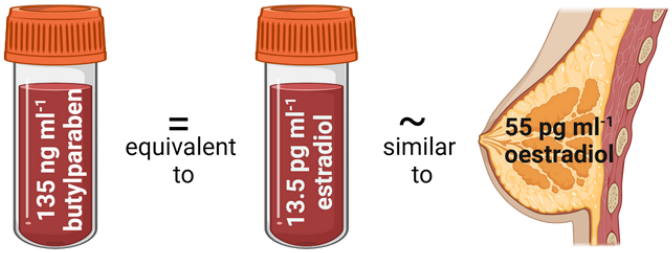

Figure 3. In people using cosmetics containing butylparaben levels as high as 135 ng ml^{-1} were measured in the blood [54]. After adjusting for the weaker activity of butylparaben, this is equivalent to having 13.5 pg ml^{-1} of oestradiol. With normal levels of oestradiol in the breast tissue being about 55 pg ml^{-1}, this suggests that levels of butylparaben relevant to human exposure may have oestrogenic effects, especially when considering mixtures [11]. Created with BioRender.com

multiple parabens are present their activity can be added together, as they act with the same mechanism, resulting in oestrogenic effects in breast cancer cells [55]. The same additive effect was also observed for cocktails of parabens with other EDCs, including other preservatives used in cosmetics [41,42].

Parabens may also show oestrogenic properties by acting through other mechanisms that do not require direct binding to the ER [49]. These include increasing the expression (or production) of hormone receptors [39,46] or interfering with the synthesis of oestrogen [43,47,48]. Concentrations of parabens, comparable to levels measured in breast tissues, may increase the expression of oestrogen and progesterone receptors, suggesting that they may be implicated in breast cancer at biologically relevant doses [39]. Parabens may also increase oestrogen production in breast cancer cells, whilst reducing it in non-cancerous breast cells [2]. In addition to this, parabens may also block the conversion of oestradiol to the weaker form (oestrone), thus increasing oestrogen levels [43]. This mechanism may be particularly relevant in post-menopause, when oestrogen levels in the breast are regulated by the breast tissue [2], and no longer by the ovary, especially considering that parabens can accumulate in the breast [30–32].

In addition to cell proliferation, parabens may prevent the death of cancer cells (evasion of apoptosis) [38] and increase the invasion and migration of breast cancer cells [40,44] , which are essential for the spread of the tumour to other parts of the body.

5.2 Animal studies

Exposure to EDCs with oestrogenic activity can be particularly harmful during certain life stages where we may be more susceptible to chemicals (read our Critical Windows of Susceptibility for Breast Development review). In some of these stages, the breast may also be more sensitive to hormonal interference as it undergoes rapid development [56].

Studies in animals have revealed that exposure to parabens during in utero development and puberty may affect the mammary gland and increase the number of terminal end buds (TEBs), which are usually the site where tumours start [57,58]. During pregnancy and lactation (breastfeeding), parabens may alter the morphology of the maternal mammary gland [57,59], whilst in adult female rodents they may increase the risk of mammary tumour and metastasis (spread of cancer cells to other tissues) [58].

5.3 Epidemiological studies

Whilst cell and animal studies suggest a possible link between parabens and breast cancer, human studies (also known as epidemiological studies) are largely inconclusive. One study showed a higher risk of breast cancer for women with the highest levels of parabens, especially for healthy-weight individuals (BMI < 25 mg/m^2) [60]. In another study exposure to parabens was negatively associated with breast cancer in postmenopausal women [61], whilst a third study found no link between the chemicals and the disease [62].

The differences in the results across these studies may be explained, at least partially, by the different methodologies used. For instance, in one study current levels of EDCs were compared with previous cancer diagnoses [62], whilst another study used parabens levels pre-diagnosis [61]. A fourth study considered whether the effect of parabens on breast cancer risk is different based on DNA methylation [63], a process where methyl groups (Me) are added to the DNA. When the DNA has a high number of methylated genes is called "hypermethylated", whilst "hypomethylation" is when the DNA has a lower number of methylated genes (Figure 4). DNA hypomethylation is a characteristic of breast cancer and it can increase DNA instability making carcinogens more potent. In this study, exposure to parabens was found to increase breast cancer risk in women with DNA hypomethylation, compared to participants with hypermethylated DNA [63].

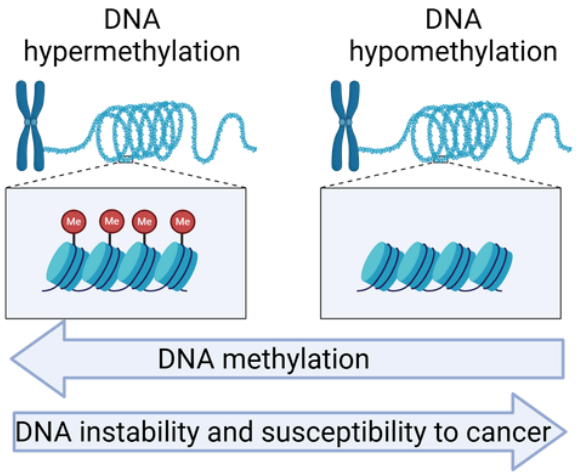

Figure 4. DNA hypermethylation is when the DNA has many methyl (Me) groups attached to it, while hypomethylation is when the DNA lacks most of the methyl groups. With decreasing DNA methylation the DNA instability and susceptibility to cancer increase. Created with BioRender.com

A few epidemiological studies have also evaluated exposure to parabens in relation to other breast cancer risk factors, such as hormone levels and puberty onset. In premenopausal women, parabens, and mixtures of these with other EDCs, were shown to increase oestrogen and progesterone levels, which may influence breast cancer risk [64]. Another study found that exposure to parabens during childhood may be linked to early puberty, which may then increase breast cancer risk later in life [20,21].

Overall, current studies present many limitations, such as evaluating exposure levels only after diagnosis and not considering all the possible risk factors that may influence breast cancer [60,62,63]. Studies that measure exposure years before diagnosis should be preferred when trying to determine if there is an association between paraben exposure and breast cancer.

Table 1. List of parabens and their regulatory status in the EU and UK, according to the Cosmetic regulations and REACH framework. This includes, whether parabens are officially recognised to have endocrine disrupting properties; whether they are allowed in cosmetics (Annex V) or banned (Annex II); whether they are in the Candidate List of Substances of Very High Concern (SVHC).

Paraben*	Endocrine disruptor** [67]	EU cosmetic regulation [70,71]	UK cosmetic regulation [66,72]	EU Candidate List of SVHC [69]	UK Candidate List of SVHC [68]
para-Hydroxybenzoic acid	-	Annex V	Annex V	No	No
Methylparaben	Under assessment (EU)	Annex V	Annex V	No	No
Ethylparaben	-	Annex V	Annex V	No	No
Propylparaben	Yes (EU)	Annex V	Annex V	No	No
Isopropylparaben	-	Annex II	Annex II	No	No
Butylparaben	Yes (EU, UK)	Annex V	Annex V	Yes	Yes
Isobutylparaben	Yes (EU)	Annex II	Annex II	Yes	No
Pentylparaben	-	Annex II	Annex II	No	No
Phenylparaben	-	Annex II	Annex II	No	No
Benzylparaben	-	Annex II	Annex II	No	No

*other parabens may exist; ** not all parabens have been evaluated.

6. Regulations

Paraben regulations in the UK are largely consistent with the current EU stance, as they were introduced before Brexit (Table 1). In 2014, five parabens were banned from cosmetics (Cosmetic Regulation, Annex II), due to insufficient information on their safety [65].

On the other hand, para-hydroxybenzoic acid and 4 parabens (methylparaben, ethylparaben, propyl-paraben and butylparaben) are allowed preservatives in cosmetics and personal care products (Cosmetic Regulation, Annex V) [66]. This is concerning because butylparaben and propylparaben have been officially recognised to be EDCs by the EU. In 2020, butylparaben was also added to the Candidate List of Substances of Very High Concern in the EU and UK (SVHC) [67,68]. The Candidate List is part of REACH, a regulatory framework separate from the Cosmetic Regulation, and contains chemicals selected to be phased out due to their harmful effects [68,69].

7. Conclusion

Parabens are EDCs used as preservatives in cosmetics, personal care products and occasionally in food. Exposure to these chemicals is widespread in the population and higher for women, possibly due to the use of cosmetics. Parabens can be absorbed through the skin and have been measured in many body fluids and

tissues, including cancerous and non-cancerous breast tissue. They can affect hormones by mimicking oestrogen and binding to its receptors, or by interfering with its levels. While some studies have shown that parabens have oestrogenic effects only at high concentrations, others have observed negative effects at doses relevant to human exposure, especially when in mixtures with other parabens or EDCs. In animals, exposure to parabens during in utero development, puberty and pregnancy has been linked to changes to the mammary gland and an increased risk of mammary tumours. Whilst laboratory studies suggest that parabens may play a role in breast cancer development and progression, human studies are limited and so far inconclusive on the link between parabens and breast cancer. Nonetheless, there is enough evidence that parabens can have harmful effects to justify a precautionary approach. People can reduce their exposure by choosing paraben-free cosmetics and personal care products, but further regulations are needed to address parabens. Breast Cancer UK is calling for a phasing out of EDCs and removing them from non-essential-use products.

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About Breast Cancer UK

Who we are?

Breast Cancer UK aims to prevent breast cancer through scientific research, collaboration, education and policy change. We educate and raise awareness of the risk factors for breast cancer and provide practical information to help people reduce these risks. We campaign to ensure government policies support the prevention of breast cancer. And we fund scientific research that helps to better understand what risk factors contribute to breast cancer, and how to address them For further information on breast cancer risk factors please visit our website www.breastcanceruk.org.uk

To view this information in a more accessible format or to provide feedback, please contact us.

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