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Personalised prevention in breast cancer

the policy landscape

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Executive summary

Context

Breast Cancer Stratification: understanding the determinants of risk and prognosis of molecular subtypes (B-CAST) is a multicentre European Commission project. The overall aim of this project is to gain a better understanding of the environmental and biological factors that influence breast cancer development and prognosis. As part of the BCAST consortium the PHG Foundation has responsibility for Work Package (WP) 8: Capacity development for personalised breast cancer prevention and early detection, the aim of which is to promote the development and integration of personalised breast cancer prevention within national public health programmes.

This report describes our analysis of the current approaches to breast cancer prevention. It provides the results of our research and analysis of the discourse around personalised breast cancer prevention within public health and policy. We have focused on primary prevention and secondary prevention programmes i.e. prevention of disease development (through health promotion) and early detection (screening). We have examined policy and prevention activities at an international level wherever possible, with specific emphasis on three key countries (United Kingdom, Netherlands and Australia) to act as case studies. Although the focus is on breast cancer, it was viewed within the wider context of prevention activities for other chronic disease.

Summary of results

Determinants of risk

Breast cancer incidence varies across the globe, with higher rates recorded in many high income countries including those in western Europe. Incidence rates are continuing to increase and this is thought to be as a result of changing exposure to reproductive and lifestyle related risk factors.

Breast cancer is a multifactorial disease in that factors acting in combination lead to disease development and progression. Risk factors for breast cancer are often classified as either non-modifiable or modifiable. Non-modifiable risk factors are those that cannot be changed and comprise inherent biological factors e.g. sex, age and genetics and life events such as age of menarche, menopause, parity and age of first pregnancy. Modifiable risk factors, mainly external influences that impact on biological factors, can be further divided into those that are related to reproduction and those that are related to general lifestyle.

However, it is clear that many of these risk factors are interlinked. Although a considerable amount is known about risk factors associated with breast cancer, the mechanism and relative contribution of different risk factors to the development of disease in individuals is still not fully understood. Furthermore, breast cancer is a heterogenous disease with different subtypes and the variable impact of these risk factors on particular molecular subtypes of disease and in specific populations is currently not fully understood.

Preventative strategies

The goal of most breast cancer control programmes is to reduce the incidence and mortality from the disease. While currently we cannot completely eliminate the disease, incidence can be lowered by addressing factors that increase the likelihood of disease development and mortality through early identification and treatment.

Due to the paucity of specific interventions that have been proven to reduce incidence of disease, most breast cancer control programmes focus on early detection and screening. As part of these programmes, health education activities aim to raise awareness about risk factors, breast health and screening, in order to ensure effective early detection and diagnosis. These activities also allow for opportunistic identification and management of women at high risk due to family history or genetic predisposition. Individuals may be suspected of being at high risk due to knowledge about family history or because they are of Ashkenazi Jewish ancestry.

Medical preventative interventions such as mastectomy that reduce risk are usually made available to these high risk individuals. Provision of such interventions and the management of individuals is guided by risk assessment, which can be undertaken using a variety of tools. The types of preventative interventions and the extent to which these are made available depends on resource availability in different settings.

The policy landscape

Examination of the global and national policy landscape indicates that there is recognition that breast cancer is an important cause of mortality and morbidity and improving primary prevention is a goal of many policy makers. The main approach to prevention is through health promotion to inform and empower individuals to reduce their own risk. However, these messages are not targeted at specific at-risk groups or modulated in any way. Furthermore, policy documents aimed at general risk factors often do not identify breast cancer as an important disease for which risk could be reduced. Established screening programmes enable early detection and treatment on a population-wide scale.

Whilst preventative strategies are available for those at high/moderate risk as a result of genetic factors or family history, identification of these women remains on an opportunistic basis. In most countries pathways of care are most well established for those who are considered high risk due to possessing *BRCA1/2* mutations.

Policy discourse around personalised breast cancer prevention

Personalised prevention as a concept has gained traction in many government policy documents as evidenced by the commitment to develop methods to enable it. However, there is little discussion on specific mechanisms to deliver personalised prevention or a vision in this area especially in relation to breast cancer.

Furthermore, as evidenced in many policy documents, personalised prevention, which aims to place individual citizens at the centre of care, is often conflated with person-centred care. The latter aims to ensure that individuals needs are met and consulted in providing their care. To some extent technologies that enable personalised prevention, especially those that are more patient facing (e.g. Apps) also enable person-centred care. A distinction we make in this report is that personalised prevention is based on biological stratification of individuals in addition to considering their individual wishes and values.

Much of the dialogue around personalised prevention is centred around the contribution of genomics. This probably reflects the fact that current capabilities in endogenous biological stratification are largely only possible on the basis genetic factors. In those who do not have a significant family history or a specific mutation has not been identified, a greater understanding is needed of the contribution of genetic versus non-genetic factors. Personalised prevention in relation to breast cancer is only discussed in the context of risk stratified screening.

Conclusion

Our investigation suggests a lack of discourse at policy level around personalised prevention for breast cancer. We designed our search strategy to be sensitive rather than specific, and given the breadth of the field, it is likely not all discussion has been captured. That said, by consulting with experts we have endeavoured to ensure that key documents were not missed and are confident this study provides an illustration of the current discourse in the United Kingdom and Australia.

1. Introduction

1.1 Context

Breast Cancer Stratification: understanding the determinants of risk and prognosis of molecular subtypes (B-CAST) is a multicentre European Commission project. The overall aim of this project is to gain a better understanding of the environmental and biological factors that influence breast cancer development and prognosis. This information can then be used to develop models and tools that will allow more precise identification of individual risk of breast cancer, and, in those with disease, improved assessment of the subtype of breast cancer that is most likely to have developed. The availability of such tools may allow more individual specific information to be generated, to inform more accurate prevention and treatment strategies.

As part of the B-CAST consortium the PHG Foundation has responsibility for Work Package (WP) 8: *Capacity development for personalised breast cancer prevention and early detection*, the aim of which is to promote the development and integration of personalised breast cancer prevention within national public health programmes. Achieving this aim requires an understanding of current practice and policy in order to better assess the potential of personalised prevention for breast cancer.

1.2 Objectives

The key objectives of this review are to:

- Describe the current landscape of breast cancer prevention within health promotion and disease prevention programmes
- Investigate the inclusion of personalised breast cancer prevention within the discourse of public health and policy makers

1.3 Scope

- The project will focus on primary prevention and secondary prevention programmes i.e. prevention of disease development (through health promotion) and early detection (screening). Activities relating to treatment and prognosis will not be included
- Relevant prevention activities and policies impacting on breast cancer across the life course of women will be examined
- Policy and prevention activities will be examined at an international level wherever possible, with specific emphasis on three key countries (United Kingdom, Netherlands and Australia) to act as case studies

- Policies will be examined at a national level only
- The focus will be on breast cancer; however, it will be viewed within the wider context of prevention activities for other chronic disease

1.4 Structure of the report

This report begins with a description of breast cancer and what is currently known in relation to disease determinants. An understanding of the disease and its determinants has an impact on developing strategies for prevention and also forms the basis of informing policies to support implementation of these approaches. We then describe available approaches for prevention and early detection of breast cancer. The extent to which these approaches are used varies in different settings as does the policy environment. We begin firstly with a global overview of prevention policies followed by a more indepth analysis of the current policy environment and prevention pathway in the context of three countries (United Kingdom, Netherlands and Australia).

In the final section we describe our findings of a grey literature search to examine the current discourse and debate surrounding personalised prevention within health policy and public health. These were conducted in the context of two countries: United Kingdom and Australia. We also attempted to conduct a search of the literature for the Netherlands, but were unable to complete this within the timescale of this report.

1.5 Overview of the methodology

Several search strategies - including a customised literature search of established databases, examination of peer-reviewed literature, other public sources of information and consultation with experts were used to identify relevant documents relating to breast cancer and approaches to prevention. National policy documents and guidelines relevant to breast cancer prevention were identified for three countries (United Kingdom, Australia and Netherlands), through conducting site specific searches and in consultation with experts.

A grey literature search strategy was developed to identify policy documents, blogs or commentaries relating to personalised prevention in two countries (United Kingdom and Australia). Data sources to search were identified through consultations with in-country experts. The appendix provides details of the grey literature search strategy.

2. Breast cancer – disease determinants

Key points:

- Breast cancer is a heterogenous disease with different subtypes
- Multiple often interrelated risk factors can contribute to development of breast cancer
- The variable impact of these risk factors on particular molecular subtypes of disease and in particular populations is currently not fully understood

2.1 What is breast cancer?

All cancers arise from the accumulation of pathological alterations to the genomes of somatic cells, resulting in disruption of normal cellular networks and control pathways. Breast cancer develops as a result of cancerous growths that start in the cells of the breast and has been linked to disruption of pathways that are involved in mammary stem cell survival and self-renewal [1, 2].These alterations are likely to occur over a period of time and continue throughout the course of disease development.

Often, the first indication of disease is either through identification of abnormalities in the breast in the form of a lump or mass during a screening test or other changes in the breast (e.g. skin irritation, nipple retraction etc.). Diagnosis is usually made following clinical assessment, mammography and/or ultrasound imaging and biopsy. Treatment of breast cancer is informed by the disease stage and whether it is an invasive or non-invasive form of the disease.

2.2 Classification and subtypes of breast cancer

Breast cancer is a heterogeneous disease, with different subtypes described based on pathology and/or prognostic factors as well as intrinsic molecular characteristics. Classification is initially based on anatomical factors such as the tissue of origin (ductal, lobular cells or other breast tissue) and the degree to which it has spread. A single breast tumour can within itself be heterogeneous in origin and exist as a mixture of invasive and non-invasive cancer. Invasive breast cancer is the most common type of breast cancer, with the majority being adenocarcinomas. Table 1 provides some examples of different classifications of breast cancer and their features.

Invasive breast cancers can be further classified based on molecular characteristics such as expression of the protein human epidermal growth factor 2 (HER2) and presence of oestrogen (ER) and progesterone (PR) receptors Table 2. The pattern of expression will have an impact on prognosis. For example, cancer cells with none of these molecular features are called triple negative. Triple negative breast cancers (TNBC) are more common in younger women and generally have a poorer prognosis than other subtypes of breast cancer.

Table 1 Classification of breast cancers

Type	Features
Ductal carcinoma *in situ* (DCIS)	Ductal cells look cancerous but have not spread into surrounding breast tissue. Considered as non-invasive or pre-invasive breast cancer, but has potential to become invasive. Most women detected at this stage can be cured. DCIS cells may be tested for oestrogen receptor (ER) status.
Invasive breast cancer	Most common type of breast cancer. Starts in ducts or lobules and spreads to the rest of the breast. Can metastasise to other parts of the body. There are other less common types of invasive breast cancer that are named after features seen under a microscope. Some have better prognosis than standard invasive breast cancer whereas others have worse prognosis. Invasive breast cancer can be further sub-classified based on molecular markers.
Inflammatory breast cancer (IBC)	Accounts for 1-3% of all breast cancers. Usually there is no single lump or tumour and it is often mistaken for an infection at the early stages. Difficult to detect and tends to have a higher chance of spreading. Consequently the prognosis is not as good as for other types of breast cancers. Tends to develop at a younger age.
Paget disease of the nipple	A rare cancer that starts in the breast ducts and spreads to the nipple. Usually associated with DCIS or invasive breast cancer. Treatment requires mastectomy. Prognosis is good if invasive breast cancer is not present.
Phyllodes tumour	Rare cancer that develops in the stroma of the breast, they are usually benign malignant forms are also possible.
Angiosarcoma	Is usually a rare complication of breast radiation therapy that can develop 5-10 years after radiation. It can also be due to lymphedema. Treatment is the same as for other sarcomas.

Table 2 *Characterisation of molecular subtypes of invasive breast cancer.*
Source: American Cancer Society. Breast Cancer Facts & Figures 2013-2014

Subtype	Molecular/genetic characteristics	Approximate prevalence	Clinical characteristics
Luminal A	ER+ and/or PR+, HER2–, low Ki67	40%	Slow-growing Less aggressive Low recurrence High survival Best prognosis of all subtypes Respond to endocrine therapy
Luminal B	ER+ and/or PR+, HER2+ (or HER2– with high Ki67)	10-20%	High proliferation rates Worse prognosis than Luminal A Respond to endocrine therapy
HER2 overexpressing	Positive for the human epidermal growth factor receptor 2 (EGFR2) protein, ER-, PR–	10%	Tend to grow and spread more aggressively More likely to be high grade and node positive Poor short-term survival Targeted therapies exist
TNBC	ER–, PR–, HER2–	10-20%	Younger age at diagnosis High histologic grade Higher rates of distant recurrence after surgery Poor short-term prognosis Lack targeted therapy

ER+/–, oestrogen receptor positive or negative; PR+/–, progesterone receptor positive or negative; HER2+/–, human epidermal growth factor positive or negative; TNBC, triple negative breast cancer.

2.3 Incidence and mortality

Breast cancer incidence varies across the globe, with rates reported by GLOBOCAN for 2012 ranging from <24.1 per 100,000 women in parts of Africa to >64.8 per 100, 000 women in North America and Europe [3]. Highest incidence rates were reported from high income countries in western Europe, North America, Australia and New Zealand. Rates of breast cancer in most low income countries are below 33 per 100,000. Global trends indicate that the number of cases worldwide is increasing and the rate of increase is more in lower resource settings [4]. Changing exposure to reproductive and lifestyle related risk factors are thought to contribute to the increasing incidence in many countries.

Mortality rates vary more widely between countries, and are partly a reflection of access to services, with the highest rates of mortality in parts of Africa and in the Pacific islands. Early detection and treatment have resulted in mortality rates in higher income settings increasingly at a slower pace in comparison to incidence.

2.4 Overview of risk factors for breast cancer

Breast cancer is a multifactorial disease in that many factors acting in combination lead to disease development and progression. Little is known about the exact causes of the majority of breast cancers; however, research has identified several factors that influence risk of disease. These are often classified as either non-modifiable or modifiable. Non-modifiable risk factors are those that cannot be changed (easily) and comprise inherent biological factors e.g. sex, age and genetics and life events such as age of menarche, menopause, parity and age of first pregnancy. Modifiable risk factors, mainly external influences that impact on biological factors, can be further divided into those that are related to reproduction and those that are related to general lifestyle. However, it is clear that many of these risk factors are interlinked.

The evidence base relating to many of the non-modifiable risk factors for breast cancer is more robust in comparison to the modifiable risk factors. Much of the difficulty with the latter stems from inherent problems of measuring exposures consistently and the fact that the outcomes that are examined (incidence or mortality) occur late in the disease pathway. This also means that little is known about how moderation of these factors impacts on risk. The fact that most studies tend to examine the impact of a single exposure variable (e.g. physical activity or alcohol consumption) as opposed to a combination of factors, means that little is known about the relative impact of different risk factors or their combined influence on disease development and progression.

Below we describe risk factors for which there is a high degree of consensus in support of an association with breast cancer and the gaps in knowledge in relation to them.

2.5 Non-modifiable risk factors

Age

The risk for breast cancer increases with age, with risk doubling each decade until menopause after which the rate of increase slows [5]. The incidence of breast cancer is more common after the menopause, with most breast cancers diagnosed after the age of 50 [6] and fewer cases diagnosed in women under 40. Women under 40 are known to have more proliferative disease, worse prognosis, and higher mortality than among those over 40. Though there is data about the incidence and prognosis of breast cancer in younger women, findings regarding associations between breast cancer risk factors and younger age at diagnosis have been inconsistent. This is partly due to the lack of representation of younger women in research studies (due to the lower incidence) as well as variable definitions for what age group represents 'younger women' [7].

Being female

Breast cancer is more common in women than men, possibly due to the increased volume of breast tissue and level of the hormones oestrogen and progesterone which are associated with breast cancer cell proliferation.

Family history of breast cancer

Family history refers to past medical history of relatives who have developed breast cancer, and is assumed to reflect the consequences of genetic susceptibilities, shared environment, and common behaviours. Having one or more first degree female relatives (i.e. mother, sister or daughter) with a history of breast cancer is strongly correlated with the risk of developing breast cancer [8]. Risk is also increased for those who have second degree female relatives with breast cancer, a relative who developed bilateral breast cancer before the menopause, a brother or father with breast cancer, or two or more close blood relatives with breast or ovarian cancer. Risk associated with differing scenarios of family history varies, with higher risk conferred by having a first degree female relative who developed breast cancer.

Genetic variants

Certain germline DNA mutations predispose women to breast and ovarian cancer. The most common cause of hereditary breast cancer is inherited mutations in the *BRCA1* and *BRCA2* genes, which can lead to 45-80% lifetime risk [9, 10]. Mutations in other genes: *CHEK2, PALB2, ATM* genes, *PTEN, TP53, CDH1* and *STK11* also increase risk of developing breast cancer, but not as much as *BRCA* gene mutations, they are also rarer in familial forms of the disease [11, 12]. Though these mutations are strong predictors of breast cancer, they are rare in most of the population (*BRCA* mutations are more common in Ashkenazi Jewish people). They are present in only 5-10% of all women with breast cancer and are not seen in a majority of the cases of women with a first-degree relative with breast cancer.

Over the last decade, genome-wide association studies (GWAS) have been used to discover over 180 low-penetrance single nucleotide polymorphisms (SNPs) that individually confer only a modest increment of risk but in combination can contribute to a relatively substantial increase in breast cancer risk [13, 14, 15]. SNPs are common genetic variants, and each individual may have differing combinations of them influencing their individual polygenic risk of developing breast cancer. The cumulative risk conferred by a number of SNPs is summarised using polygenic risk scores (PRS). It is estimated that the lifetime risk of cancer for women below the first and above the 99th percentile of the PRS is 3.5 % and 29.0 %, respectively [16]. Furthermore, these low penetrance SNPs may modify risk in *BRCA1/2* carriers[17].

The various types of variants identified and linked to breast cancer, to date, explain only 50 % of the heritability of breast cancer and hence much of the genetic contribution to breast cancer aetiology remains unknown [13].

Race and ethnicity

The most studied ethnic groups in relation to breast cancer are Caucasian (United States and European) and to some extent African American women. It has been consistently observed that the overall incidence of breast cancer among African American women is lower than that for Caucasian women. However, compared to Caucasian women, breast cancer occurs in younger African American women, presents at a more advanced stage with more aggressive histologic characteristics, and is associated with a worse survival for all stages and at all ages [18]. However, it is unclear if this reflects a true effect in this population or is a reflection of access to care. Comparable breadth of evidence does not exist for the relationship of breast cancer with other ethnicities.

Personal history of breast cancer

Occurrence of breast cancer in one breast is associated with a risk of developing cancer in the other breast or in another part of the same breast (in contrast to the recurrence/return of the first cancer) compared to those who have never been diagnosed with breast cancer. The risk is higher if the diagnosis was made below the age of 40. These women have almost 4.5 fold increased risk of subsequent breast cancer. Mutations in *BRCA1* and *BRCA2* genes contribute to some of the excess risk in younger women.

Dense breast tissue

Breast density is measured by the appearance of breast tissue on a mammogram, which varies depending on tissue composition. Individuals with dense breasts (on a mammogram) have more glands, ducts and supportive tissue and less fatty tissue. Increased breast density on mammographic imaging is associated with an increased (up to four-fold) risk of developing breast cancer [19].

Breast density is influenced by other factors such as age, BMI, parity, menopausal status as well as endogenous and exogenous hormonal factors [20]. It has been proposed that endogenous (such as genetic damage and activation of growth factors) and exogenous factors (such as stromal response to environment) or an interaction of the two can contribute to differences in breast density. The mechanism by which breast density influences risk is not well understood. There is also no clarity about the role of breast density in the aetiology of tumour subtypes or the interactions with other risk factors including ethnicity and environment.

Benign breast conditions

Though most benign breast conditions are not a risk factor for developing breast cancer in the future, benign conditions with certain histological characteristics such as atypical (with cell abnormalities) ductal and lobular hyperplasia are most commonly associated with breast cancer (up to five-fold increase in risk) [21].

Endogenous hormones and reproductive features

It is recognised that women's lifetime exposure to circulating steroid hormones (oestrogen and progesterone) are related to their risk of developing breast cancer. Factors influencing increased hormone levels include early menarche (menstruation), not having children or late age at first full term pregnancy (both of which can also be by choice) and late menopause [22]. Longer hormone exposures due to early menarche and late menopause influence the length of time that women undergo cycles of hormone-induced cell proliferation and therefore increasing the potential for DNA-mutation during cell division. It is hypothesised that early first full term pregnancy (before 35 years of age), influencing the endogenous hormone balance, can make the ductal epithelial cells of the breast less susceptible to carcinogens [23].

The role of hormonal exposures in the aetiology of breast cancer subtypes, including that for various subgroups, over the life course is poorly understood. There also needs to be further research exploring the underlying pathways that explain specific differences in pre- and postmenopausal breast cancer. The natural history of disease varies in pre- and post-menopausal women.

2.6 Modifiable risk factors

Physical activity

The general consensus is that physical activity reduces the risk of breast cancer [24, 25, 26]. The World Cancer Research Fund (WCRF) in a recent report concluded that there is consistent evidence that physical activity reduces the risk of post-menopausal breast cancer; however, the evidence for pre-menopausal breast cancer was limited [27]. Limitations in the evidence arise from that fact that menopausal status of women is often not reported in many studies. This together with the fact that a variety of measures have been used to collect information on physical activity mean little is known how different levels of physical activity impact on risk.

Adult body mass index (BMI), weight gain and height

The association between a number of physical characteristics (BMI, weight, height, waist circumference etc.) and breast cancer have been examined. There is consistent evidence that excess weight and obesity, especially in adulthood are associated with post- menopausal breast cancer. The evidence for the relationship with breast cancer across other age groups is more ambiguous.

A high BMI (BMI>25kg/m^2) is a recognised risk factor for post-menopausal breast cancer. Women with a high BMI (BMI>25kg/m^2) are at about 1.5 times higher risk while obese (BMI>30kg/m^2) women are at about two times higher risk for breast cancer compared to lean women [28]. In postmenopausal women, fat tissue is the largest source of oestrogen and, there is speculation that this may be the mechanism linking excess weight and breast cancer. The report by the WCRF [27] agrees; their analysis indicates that greater BMI throughout adulthood is associated with an increased risk of postmenopausal breast cancer.

Studies also indicate that the pattern of weight gain may influence risk, with weight gain in adult years as opposed to at a younger age leading to an increased risk [29]. The WCF's analysis indicates that high BMI and obesity between the ages of 18-30 reduces risk of both pre- and post-menopausal breast cancer. The pattern of fat accumulation such as excess fat on the waist area in comparison with excess fat in the hips and thighs may also influence risk. Factors that lead to greater adult height are also thought to increase risk of breast cancer.

Alcohol consumption

Numerous studies show that even moderate consumption of alcohol is associated with increased risk of breast cancer [30]. Systematic reviews provide evidence that the relative risk of breast cancer increases by 7.1% for each additional 10 grams per day intake of alcohol even after statistical adjustment for smoking [31]. However, there seems to be no further increase in risk beyond 60g of alcohol per day. A prospective study (Nurses' Health Study) which followed more than 100, 000 women over 28 years further showed that even low levels of alcohol consumption in both early and later life increases the risk of breast cancer risk [32].

Despite much research into the association of alcohol with breast cancer risk, the relationship of alcohol consumption with breast cancer subtypes, population subtypes, life-stages and interaction with risk factors such as diet are still unclear.

Exposure to radiation

Women who have had diagnostic or therapeutic radiation therapy to the chest or breasts (e.g. for Hodgkin's lymphoma, scoliosis, tuberculosis), particularly before the age of 30, have been shown to be at a higher risk of developing breast cancer later in life (by more than four-fold) [33]. Many epidemiological studies suggest that radiation risk is associated inversely with the age at exposure; exposure during puberty confers the greatest risk and menopause the lowest.

Repeated high radiation imaging scans such as CT scans have increased significantly over the last two decades and provide radiation exposure at levels associated with increased cancer risk. Children and adolescents receiving high radiation imaging scans (e.g. CT scans, fluoroscopy) are at even higher risk due to the greater sensitivity of their tissue as well as higher cumulative lifetime dose over the remainder of their life. Additionally, lower dose exposures, including serial radiographs for scoliosis, especially in children and adolescents with a family history of breast cancer, have been shown to be associated with increased risk of breast cancer.

It seems to be definitive that higher level radiation exposure at a younger age is linked to increased risk of breast cancer. However, it is unclear how the cumulative effect of low dose long term radiation (e.g. X-rays) impacts on breast cancer risk, particularly in those without a family history of breast cancer, and what the interactions are with other genetic and environmental risk factors.

Hormonal birth control

Hormonal birth control refers to either oral contraceptive pills (OCP) or other contraceptives that contain or release hormones. Most studies into breast cancer have focused on oral contraceptive pills, especially those that are a combined formulation of oestrogen and progesterone. These suggest that recent (within the prior year) use of oral contraceptive pills increases the risk of breast cancer (Odds Ratio, 1.5; 95% CI, 1.3–1.9) relative to never or former OCP use but this risk begins to decline shortly after stopping use of OCP and the risk disappears 10 years after discontinuation [34, 35]. No relationship was found between risk and duration of use but the small increase in breast cancer risk is greater among women who begin using OCP before the age of 20 or before first pregnancy [34]. Studies have begun to assess relationships between formulations of the combined pill, as well as the impact on different subtypes of disease.

Studies examining the association between progestin-only formulations (including progesterone only oral contraceptives, progesterone depot, injectables, levonorgestrel Mirena users, implantable and intrauterine devices) have concluded that current evidence shows they do not impact on risk [36].

More research is required to identify the underlying mechanisms that regulate steroid hormone action (including that for oestrogen and progesterone) across life stages in the normal breast and in breast cancer, as well in the subtypes. There is also a lack of research that examines differences in the pre and post- menopausal breast that lead to sensitivity to exogenous steroids including exogenous post-menopausal hormones.

Pregnancy-related factors

As outlined above, some pregnancy-related factors impact on risk of breast cancer through their influence on endogenous hormones. Factors that lower risk include early age at first full term pregnancy and increasing number of births.

Breast feeding

Breast feeding is recognised as being protective against breast cancer, especially if the duration is 12 months or longer. In most studies breastfeeding is defined as "ever given breastfeeding regardless of duration" and the outcome was usually invasive breast cancer [37]. Studies are beginning to examine association between breast feeding and molecular subtypes of breast cancer, but these have not as yet produced conclusive results.

Postmenopausal hormones

Hormones commonly used to treat symptoms of menopause are oestrogen and progesterone. As with oral contraceptives these hormones are often taken together, although some women are given oestrogen alone. Several studies have assessed the links between the use of hormone replacement therapy (HRT) and breast cancer. Evidence suggests that combined therapy increases risk and is greater for those women who start using HRT soon after the onset of menopause, but the increased risk decreases within five years of discontinuation of HRT use. There is conflicting evidence on the effects of oestrogen only therapies on breast cancer risk [38].

Other risk factors

In addition to the risk factors outlined above, research has identified further modifiable exposures that may be linked to breast cancer, but the evidence base is not yet robust enough to provide conclusive evidence of their impact. These include tobacco smoke, exposure to a light at night, diabetes mellitus, inflammation, environmental chemical exposure, height, diet and childhood weight gain.

2.7 Impact of risk factors across the life course

The breast develops and changes throughout the lifetime of a female; there are times when the breast is susceptible to exposures that can increase the risk of developing breast cancer. From birth to puberty there is gradual growth of the gland but with the onset of puberty there is exponential growth in response to endogenous oestrogen and progesterone hormones. There is progressive differentiation of the gland in each successive menstrual cycle, and further development of the gland during pregnancy and lactation. Following menopause the gland regresses due to reduction of ovarian hormones.

It has been shown that risk accumulates rapidly from menarche to first birth; the rate slows after each birth and early menopause reduces subsequent risk [39, 40]. This probably relates to the fact that the main periods of breast development are during puberty, pregnancy and lactation, with glandular tissue atrophying after menopause. Given that the response of breast tissue to hormonal and environmental factors is likely to vary at these different stages, it is likely that the effect of risk factors is differential at these key life stages.

It is recognised that different factors may have an influence on pre- and post-menopausal breast cancer; however, the exact factors that impact at these different life stages is unclear. This is due to the fact that many studies have not stratified by menopausal status. Furthermore, there are few studies examining the impact of environmental risk factors across the other life stages.

2.8 Summary

Although a considerable amount is known about risk factors associated with breast cancer, the mechanism and relative contribution of different risk factors to the development of disease in individuals is still not fully understood.

A challenge in understanding the impact of various risk factors stems from difficulties in measuring exposures consistently in studies and the fact that the outcomes that are examined (incidence or mortality) occur late in the disease pathway. The interrelationship between risk factors also creates challenges; for example in investigating post-menopausal breast cancer, consideration also needs to be given to factors such as the use of HRT, number of reproductive cycles and age at which children were born. Furthermore, there is considerable interaction between these risk factors, resulting in a complex picture of their involvement in disease development. The variable impact of these risk factors on particular molecular subtypes of disease and in particular populations (e.g. high risk individuals due to genetic susceptibility) is currently also not fully understood.

3. Current approaches to prevention

Key points:

- Most preventative strategies are aimed at individuals later in life and are focused on early detection.
- Preventative strategies may be instigated in those at higher risk due to family history or genetic susceptibility. However, identification of such individuals in most settings is opportunistic.
- A number of risk prediction tools and models are available; however, their use in clinical practice is in limited settings.

3.1 Overview of breast cancer control

The goal of most breast cancer control programmes is to reduce the incidence and mortality from the disease. The risk of developing breast cancer can be reduced, but not eliminated, and current preventative activities with relation to breast cancer incidence are limited to general health messages regarding lifestyle and other modifiable risk factors.

Due to the paucity of specific interventions that have been proven to reduce incidence of disease, most breast cancer control programmes focus on early detection and screening. As part of these programmes, health education activities aim to raise awareness about risk factors, breast health and screening, in order to ensure effective early detection and diagnosis. These activities also allow for opportunistic identification and management of women at high risk due to family history or genetic predisposition. Individuals may be suspected of being at high risk due to knowledge about family history or because they are of Ashkenazi Jewish ancestry. Medical preventative interventions such as mastectomy that reduce risk are usually made available to these high risk individuals. Provision of such interventions and management of individuals is often guided by risk assessment, which can be undertaken using a variety of tools.

The types of preventative interventions available are described below; the extent to which these are made available depends on resource availability in different settings.

3.2 Preventative interventions

Promoting lifestyle modification

As outlined in the previous section, several lifestyle factors have consistently been associated with breast cancer. Diet, physical activity and alcohol consumption are particular focal points for health promotion and education messages. The rationale for focusing on these factors is:

- They apply to all women, since all are at some risk,
- These risk factors are similar to those that help prevent other chronic conditions such as diabetes and heart disease
- There is general consensus that activities aimed at addressing these modifiable risk factors can have an impact on reducing risk and thereby the incidence of breast cancer.

Consequently, health promotion and education messages encouraging maintaining a healthy weight, regular exercise, reduced alcohol consumption and a balanced diet are included as part of most cancer and breast cancer prevention policies and strategies.

Some studies have shown that risk in *BRCA1/2* carriers is increased with weight and smoking and reduced with physical activity. Studies have also shown that risk accumulates over time and can be affected by the time period of exposure to adverse factors. For example, rates of weight gain during premenopausal periods can have an impact on risk. However, the lack of evidence from randomised control studies examining specific interventions aimed at different strata means that current practice is not to give differential advice to different risk strata.

Chemoprevention

Chemoprevention is defined as 'the use of pharmacologic or natural agents that inhibit the development of invasive breast cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of premalignant cells in which such damage has already occurred' [41]. There are two types of pharmacologic agent – selective oestrogen receptor modulators (SERMs) such as tamoxifen and raloxifen, and aromatase inhibitors such as exemestane. SERMs work by blocking the effect of oestrogen on cells. Aromatase inhibitors reduce the levels of circulating levels of estradiol by preventing the conversion of androgens to oestrogens.

The use of SERMs in reducing risk has been investigated in many randomized control trials (RCTS). Most of these trials involve women who are at increased risk; however, some have assessed women at average risk [42]. These studies have shown that chemoprevention can reduce risk 20-76% depending on the subtype of disease. Due to the different impact and side-effects of these drugs, different agents are prescribed to individuals based on factors such as their risk, age, race and prior hysterectomy. Even though chemoprevention can be an effective means of reducing risk, its uptake has been shown to be low [43].

Risk reducing bilateral mastectomy

This involves removal of as much healthy tissue as possible from both breasts. The operation greatly reduces, but does not eliminate, the risk of future breast cancer. This intervention is usually offered to women who have a strong family history of breast and/or ovarian cancer and to women with known *BRCA1/2* mutations. Studies suggest that this procedure reduces incidence by 90%.

Oophorectomy

As with mastectomy, oophorectomy is usually only offered to those women who are at high risk due to a genetic predisposition for breast and ovarian cancer. The procedure reduces risk by 37-42% and has a greater effect in women who may develop ER-positive breast cancer.

3.3 Early detection

The structure of early detection and screening programmes varies globally. This ranges from public education and awareness about breast health and cancer, along with clinical history and opportunistic clinical breast examination (CBE) to organised programmes to target specific at-risk populations and offer mammographic screening. In those countries with an organised breast screening programme, the target population is usually women aged 40 and over, due to the increased risk in this age group.

Breast awareness

Early detection programmes rely on raising awareness of breast health including education on risk factors, availability of screening and symptoms of breast cancer for both the public and medical professionals. Awareness raising usually occurs in collaboration with non-governmental organisations such as cancer charities in order to effectively disseminate key messages. Self-breast examination is also usually promoted to encourage breast health awareness and early detection.

Clinical breast examination

Physical examination of the breasts by trained health care professionals may be offered as part of routine health checks or to women who have breast complaints. They are sometimes used as part of a screening programme in low resource settings.

Mammographic screening

Breast X-rays (mammograms) are the most common screening test used as part of screening programmes and, in some cases, are offered in conjunction with a clinical breast examination. The exact demographic of women invited for screening varies internationally as does the interval between screening (1, 2 or 3 years). If an abnormal finding is detected on the mammogram, further assessment is carried out; this usually involves diagnostic mammography, ultrasound and clinical assessment to determine if pathology is present. Those at high risk, either due to family history or genetic susceptibility, may be offered enhanced screening using magnetic resonance imaging (Breast MRI) in addition to mammographic screening.

Organised mammography screening programmes are the only population-based method that has been associated with reductions in breast cancer mortality. However debate continues regarding their use. Due to the substantial investment required in providing a mammography screening programme, it is usually only practiced in high income settings. Certain countries have implemented large scale opportunistic screening programmes using mammography - the clinical effectiveness of such approaches are yet to be determined.

3.4 Risk prediction tools

In cancer, assessment of risk is usually undertaken using tools based on underlying risk prediction models. These models aim to predict risk based on a combination of known or measured characteristics and can be used to predict risk of current disease in those with symptoms or to predict risk of future disease in asymptomatic individuals. The former is primarily used to guide further investigation whereas the latter is used to provide information on risk and to facilitate decisions on a specific intervention to be made. Here we concentrate on the latter and the use of risk prediction models in prevention.

Several tools are available for use by the general public and health professionals to assess breast cancer risk. They each have different strengths and weaknesses, as they take a different set of risk factors into account and are based on different risk prediction models and algorithms.

Models are often categorised based on the risk factors they incorporate and the type of information they provide. Some models have been developed based mainly on hormonal and environmental factors whilst others are based mainly on family history. Absolute risk prediction models predict risk of breast cancer over time (e.g. 5 year, 10 year or lifetime) and are relevant to all women. They aim to predict if a woman in the population with a particular set of risk factors will develop breast cancer. Several models perform this function, and tools for use in a clinical setting as well as for the use by the general public are available. Gene carrier status models predict the probability that a person carries a mutation in the *BRCA1/2* genes and can act as a useful clinical decision aid tool as to whether to perform a genetic test. Some models estimate both absolute risk and gene carrier status.

Research institutes, health charities and governmental organisations have developed these tools and models. Information on how the tools were developed and the underlying model is available for a limited number of them.

Tools available for risk prediction can be broadly divided into two groups:

- Online risk assessment tools aimed at the general public
- Risk assessment tools used by health care professionals

Some risk assessment tools are available via the Internet for use by the public. These tools allow individuals to input personal risk information in order to obtain an indication of their level of risk in comparison to the wider population. They generally do not provide information on gene carrier status. As many aim to increase awareness, they also provide suggestions on ways to reduce risk based on the information provided and education on screening options. In many cases, information relating to tool development, limitations and underlying models is not available, and for the large part they have not been validated or evaluated.

Risk assessment tools developed for health care professionals may be available online or in the form of software. Some of those available online may also be accessed by the public. In contrast to the tools for the public, these risk prediction tools allow for more detailed input such as comprehensive family history, genetic factors and non-genetic factors that modify individual cancer risk, and work is ongoing to incorporate a wider range of risk factors into these models. The most commonly used tools are described below and Table 4 provides a summary of the risk factors they consider and their uses.

Gail model

The Gail model, also referred to as BCRAT/NCI, is an example of a model based on hormonal and environmental risk factors. It is one of the earliest models and was developed by researchers at the National Cancer Institute in the US and the National Surgical Adjuvant Breast and Bowel Project [44]. It was initially developed based on data from the Breast Cancer Detection Demonstration Project (BCDDP). It is intended for use in women 35 years or older and predicts risk of invasive breast cancer over time. Absolute risk of disease can be calculated for 10, 20 or 30 year intervals.

Since its initial development, it has been modified and extensions developed in order for it to be applied to different ethnicities. This includes African-American women (also known as the CARE model), Hispanic and Asian women. A version of the model that incorporates breast density data (Chen model) has also been developed. The initial model has been validated on an external dataset, as have some of the extensions. However, they may require further validation in additional populations (e.g. including younger women, different Hispanic populations) to assess generalisability.

The Claus model

This model was developed by researchers at Yale University based on cohort of women from the Cancer and Steroid Hormone Study (CASH) [45]. It is intended for use in women with at least one female first or second degree relative with breast cancer and estimates lifetime risk of invasive breast cancer and DCIS. More specifically, it estimates risk of familial breast cancer not associated with a known susceptibility gene. It does not take into account any environmental, hormonal or genetic factors and is based solely on the number of first degree relatives with breast cancer.

Manchester scoring system (MSS)

This model was initially developed in 2004 by researchers in Manchester, UK [46] based on data from a cohort of non-Jewish families with family history of breast cancer and has since been updated using data from larger cohorts. It is targeted at those with a family history to determine their eligibility for genetic testing. It is available as computation software that provides a numerical score based on family history assessment of breast, ovarian, prostate and pancreatic cancer, age of diagnosis and taking into consideration *BRCA1/2* status of affected family members. The latest updates also incorporate histological information such as ER status and *HER2* expression in calculating risk of *BRCA1* mutations. The score can then be used to support recommendations for a *BRCA1/2* test. It has been validated on two external cohorts.

Breast Cancer Surveillance Consortium Risk Calculator - BRCAPRO

This model was developed by researchers at Duke University and first described in 1999 [47]. This is an example of a model that performs multiple functions; it is targeted at individuals with and without family history of breast cancer and can be used to assess probability of carrying germline mutations in *BRCA1/2* genes, developing invasive breast or ovarian cancer, and the probability of developing contralateral breast cancer in individuals with a diagnosis. Mutation carrier status probability is calculated based on family history, pathological markers (e.g. ER, *HER2* status) for known cases, and published estimates of prevalence, penetrance of *BRCA1/2* and baseline rates of breast cancer in the population.

The model is updated as published information is refined. Simplified versions of the model are available that do not require extensive data input on family history or can impute parameters such as age and number of affected relatives. It is not applicable to the general population, due to the fact that the model does not take hormonal or environmental factors into account, does not address lower penetrance genes and focuses on assessing *BRCA1/2* status.

The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)

This model was developed by researchers at the University of Cambridge and first described in 2004 [48], it has since been updated. It is available as a web application that can be used to calculate risk of breast and ovarian cancer based on family history and carrier probability for *BRCA1/2* mutations. Similar to BRCAPRO it performs multiple functions. However, it is mainly used to assess women who are suspected of being at increased risk due to family history. The current version of the model does not take into account hormonal or environmental factors, but calculates risk based on extensive information on family history of breast, ovarian, prostate and pancreatic cancer, age of diagnosis, age of unaffected family members, Ashkenazi Jewish origin and information on any *BRCA1/2* testing. The model has been validated through comparison with other models but has primarily been developed using data for the UK and has not been widely evaluated in other populations.

Tyrer-Cuzick/IBIS

This model was developed by researchers at Cancer Research UK and first described in 2004 [49]. As with the two models, provides an estimate of the probability of a germline mutation in *BRCA1/2* genes and the risk of breast cancer. It is also available as the IBIS software. However, in contrast to the previous two models, it takes hormonal and environmental factors into account. It has been compared with Gail, BRCAPRO and Claus models in cohort studies and shown to have better calibration when applied to high risk populations based on family history.

Table 4 below summarises the most commonly used tools, the factors they consider and their uses.

Table 4 *Examples of the most commonly applied tools, the models they are based on, the risk factors they consider and their uses*

Tool	Types of risk prediction/ output	Risk factors	Uses
Breast cancer risk assessment tool/GAIL	Absolute risk prediction	Age, personal medical history, reproductive history, number of first degree relatives with breast cancer, tumour pathology.	Breast cancer risk, inform decision making about chemoprevention strategy, and determine eligibility for clinical trials.
CLAUS	Lifetime risk of invasive breast cancer	Family history of breast or ovarian cancer limited to first and second degree relatives.	Breast cancer risk in those with a family history.
Manchester scoring system (MSS)	Gene carrier status	Affected relatives with breast, ovarian, pancreatic, prostate cancers, *BRCA1/2* mutations, pathology and histologic findings.	Numerical score for recommendation for genetic testing in those with a family history.
Breast Cancer Surveillance Consortium Risk Calculator (BRCAPRO)	Absolute risk prediction Gene carrier status	Age, race/ethnicity, status of breast or ovarian cancer for all relatives, age of unaffected relatives, breast density, history of breast biopsy, molecular markers.	Assess probability that an individual carries a mutation in *BRCA1/2*, future risk of breast or ovarian cancer for unaffected individuals, risk of contralateral breast cancer for affected individuals.
BOADICEA	Absolute risk prediction Gene carrier status	Extensive family history of all affected and unaffected relatives, *BRCA1/2* and polygenic component, pathology markers, Ashkenazi Jewish ancestry.	Assess individual breast cancer risk and assessing probability that an individual carries a mutation in *BRCA1/2*.
Tyrer-Cuzick Model /IBIS	Absolute risk prediction Gene carrier status	Age, reproductive factors, height and weight, history of benign breast conditions, use of HRT, limited family history to first and second degree relatives with breast cancer, *BRCA1/2* and Ashkenazi Jewish ancestry.	Assess individual breast cancer risk and assessing probability that an individual carries a mutation in *BRCA1/2*.

Ethical, legal and regulatory issues

As risk stratification tools move from a research setting into clinical practice, the legal and regulatory status of these tools is likely to become increasingly important. Two different legal frameworks apply – the laws governing the processing of personal data, and those regulating how medical devices are developed and manufactured. The legislation governing both data and devices are set to change over the next few years through the introduction of European legislation.

Data Protection

Data protection law impacts upon risk stratification tools in two potential ways: through regulating the type of data processed and the mechanism by which it is processed. Under current data protection regulation, the permissibility of data processing depends heavily upon the purpose for which risk stratification is performed. Where tools are used within a healthcare paradigm, existing exemptions for processing medical data will usually apply. However, if consumers access such tools on a direct to consumer basis, the legal status of data processing will be less clear, particularly if data is transferred across national borders, since some countries within Europe apply additional protections for the processing of genetic data.

This position is likely to change under a forthcoming European Regulation (the General Data Protection Regulation [50]) that will come into force in May 2018. This Regulation protects genetic and genomic data as a special category of personal data, and also prevents the use of automated profiling if a decision is based solely on automated processing, and the impact 'produces legal effects' or similarly significant outcomes [50]. This provision could restrict the use of risk stratification tools particularly as a first-line intervention in population screening.

Risk prediction tools as in vitro *diagnostic medical devices*

Risk prediction tools incorporating software and algorithms may currently qualify as *in vitro* diagnostic medical devices under EU legislation if they are used, amongst other things, for diagnosis, prevention, monitoring, treatment or alleviation of disease and satisfy various other conditions [51]. In practice, technicalities around the classification of *in vitro* diagnostic devices have meant that only devices utilising results which have been generated exclusively from IVD medical devices have been regarded as falling within the Directive: on this basis, risk prediction tools have often been regarded as falling outside this legislation.

As with the processing of data, this situation is likely to change with the implementation of a revised EU *In Vitro* Diagnostic Medical Devices Regulation [51]. The scope of this Regulation covers those medical devices used '*in vitro* for the examination of specimens, including blood and tissue, solely or principally to provide information for a variety of purposes: these include the diagnosis of a congenital impairment; 'the predisposition to a medical condition or disease', and to guide and monitor treatment.

This is important in the context of risk stratification tools because the Regulation unambiguously regulates 'software' when used for determining predisposition to a medical condition or disease, including risk assessment, whether used alone or in combination. All devices utilising human genetic testing of samples will have to meet requirements for generating appropriate clinical evidence and demonstrating performance and effectiveness, before risk algorithms can be placed on the market. This will include satisfying criteria for safety and performance, with certain aspects being demonstrated in normal and affected populations. It also might be necessary to provide additional technical information including an overview of the entire system, and the interpretation methodology [51].

If the algorithms are to be used for self-testing or near patient testing by health care professionals the requirements for performance evaluation and labelling are more onerous but the Regulation excludes the use of software used for general or well-being purposes which are not classified as diagnostic medical devices.

More widespread use of risk stratification tools in the general population raises a number of ethical issues: one of the most pressing is whether the positive predictive value of the test is sufficient to ensure that the benefits from use outweigh the potential disadvantages. This might include ensuring that the risk assessment tool has been developed in ways which take account of clinically relevant differences between populations (such as ethnicity, gender); otherwise the tool may perform less reliably for some sub-groups. This is particularly important if the tool is to be used to inform decisions about future access to interventions (such as screening) or other care or treatment. Systematic bias in a tool could cause foreseeable injustices for these groups, especially if there are limited resources that are available for further care and treatment.

Advances in genomic technologies mean that it is becoming possible to generate information about the entire genome, faster and more cheaply than ever before. Future risk prediction tools may well encompass more testing in a bid to improve the accuracy and reliability of the tool. However, there is also the potential for tools to generate unexpected findings which may have clinical significance. Thus if risk prediction tools are to be implemented within the wider population, strategies need to be developed for the validation, reporting and clinical follow up of these unexpected findings. Resources will need to be developed for both professionals and patients – and for consumers (if tools are administered on a direct to consumer basis).

3.5 Summary

Cancer is recognised as a leading cause of mortality across the globe, as witnessed by the large number of countries with policies aimed at addressing this disease. Although breast cancer is the most common cancer in women [52, 53], there is wide disparity in the types and availability of preventative, diagnostic, treatment and management services. Consequently the outcomes across the world vary. Low and middle income countries suffer from a larger burden of mortality [53, 54] in comparison to high income countries. Effective early detection, diagnosis and treatment in many high-income countries have helped to reduce the burden of disease to some extent. However, it is widely acknowledged that more could be done, especially by attempting to address many of the modifiable risk factors.

Although it is recognised that exposures throughout the life course can impact on risk of developing breast cancer, most preventative strategies are aimed at individuals later in life and are focused on early detection. This is because early life exposures that impact on risk have not been well studied and interventions aimed at them are similar to those who are at low risk of developing disease and for other chronic diseases. Preventative strategies may be instigated at an earlier time point in adult life in those considered to be at high risk due to family history or genetic susceptibility. However, identification of such individuals in most settings is currently opportunistic.

The provision of preventative interventions is to some extent linked with our ability to accurately estimate risk and link factors that increase risk in individuals to appropriate interventions. It has been suggested that such risk prediction tools can be used to better tailor screening, behaviour change and preventative treatment by improved stratification of individuals. Although there are risk prediction models and tools available, their use in these areas of clinical practice is currently limited.

4. The policy landscape

Key points:

- Countries recognise the need for primary prevention of breast cancer
- The main approach to prevention is through health promotion to inform and empower individuals to reduce their own risk
- Established screening programmes enable early detection and treatment, however, the availability, structure and access to such a screening programme varies globally
- Preventative strategies are in place for those at high/moderate risk, although identification of these women is opportunistic
- Pathways of care are most well established for those who are considered high risk due to possessing BRCA1/2 mutations

4.1 Introduction

Health policy refers to decisions, plans and actions undertaken to achieve particular health goals. They can outline priorities, the role of different groups, build consensus and provide information. A range of topic areas are covered by health policies (e.g. public health or specific diseases), functioning at different levels (e.g. global health, national or local) and each affecting decisions made on the availability, nature and delivery of particular health services. Of note, although the presence of policies indicates support for particular programmes, services or interventions, they do not provide a comprehensive picture of activities that are actually implemented or the extent to which they are accessed. This section describes the policy landscape that impacts on the control and prevention of breast cancer.

4.2 Methodology

In common with most health-related policy, breast cancer prevention and control activities are influenced by policy development in different areas forming a complex picture. To reduce the complexity and for reasons of pragmatism, we have taken a two-step process to describe the national policy landscape in relation to breast cancer.

We began by examining the availability of top-down polices in key areas related to breast cancer in a global context. These encompass non-communicable disease (NCD) policy and cancer strategies and those related to shared risk factors. This approach was taken as we believe that the nature of available prevention and control activities will be influenced by policy development in these areas. The results of this analysis are described below.

In the next step, we identified national policies relating to shared risk factors, NCDs and cancer strategy and examined them in more detail in the context of three countries – United Kingdom, Netherlands and Australia. This enabled us to determine whether breast cancer is regarded as an important consideration in relation to these policy areas and whether they outline specific activities in relation to this disease.

We also attempted to identify and describe specific operational policies in relation to breast cancer prevention. Such policies relate to health promotion activities, clinical guidelines, best practice and care pathways specifically related to breast cancer prevention and control. Examination of operational policies allows description of the nature of any specific current activities that are available in these countries.

4.3 The global overview and case studies

The WHO Global Health Observatory (GHO) is the WHO's main health statistics repository for its member states and contains an extensive data set relating to a number of indicators. Data are gathered to monitor progress towards Sustainable Development Goals (SDGs) and contain indicators for specific health-related targets. Data are gathered through a variety of methods and from a number of sources by the WHO and partners in collaboration with member states [55]. As the aim is to allow comparability across countries and time, methodologies used may lead to differences with official national estimates.

In order to obtain a global overview of prevention policies, we analysed publicly available data outlining policies, strategies and action plans by country in areas relating to non-communicable diseases or risk factors related to breast cancer. The following indicator data were downloaded to provide a global overview of the availability of top-down policy in key areas:

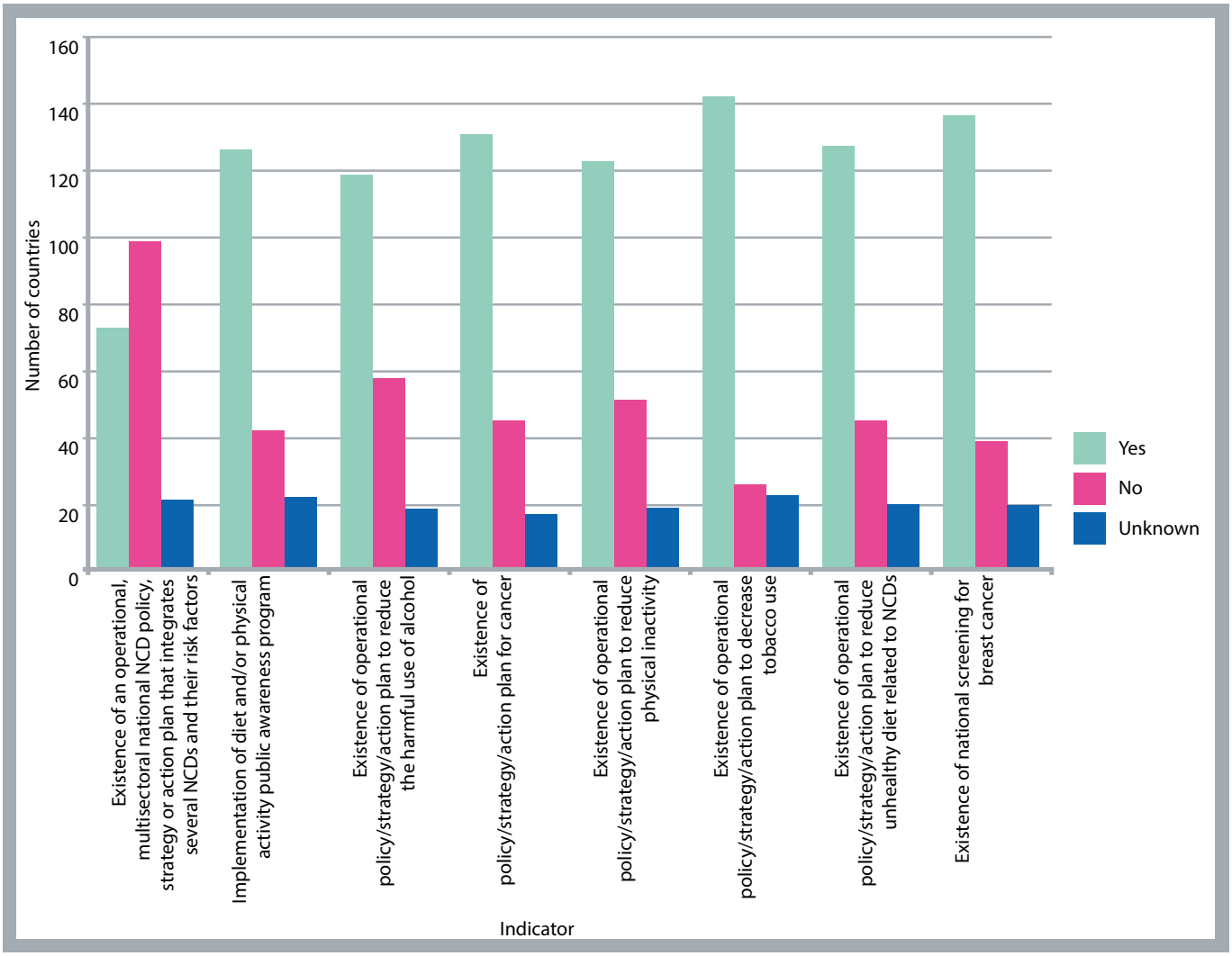
- Existence of an operational, multi-sectoral national NCD policy, strategy or action plan that integrates several NCDs and their risk factors
- Implementation of diet and/or physical activity public awareness program
- Existence of operational policy/strategy/action plan to reduce the harmful use of alcohol
- Existence of operational policy/strategy/action plan for cancer
- Existence of operational policy/strategy/action plan to reduce physical inactivity
- Existence of operational policy/strategy/action plan to decrease tobacco use
- Existence of operational policy/strategy/action plan to reduce unhealthy diet related to NCDs
- General availability of breast cancer screening (by palpation or mammogram) at the primary health care level

We chose these indicators as they allowed us to investigate the wider policy landscape through examining the existence of top-down national policies in relation to NCD, cancer and shared risk factors. Figure 1 shows the results of this analysis for 2015 and gives an indication of the number of countries that have developed action plans or strategies in these areas. We were also able to obtain data on the number of countries that have policies relating to breast cancer screening. Most countries have policies relating to NCDs and a national screening programme for breast cancer (60% or above). This reflects a general global push to tackle the burden of disease due to NCDs. However, few countries have operational, multi-sectoral national NCD policies; this applies to both low and higher income settings.

Although the data suggest that many countries have a national screening programme for breast cancer, the quality and access to such services is likely to vary. Most high and middle income countries have implemented policies for early detection of breast cancer through systematic population based screening programmes utilising mammography. This is unlikely to be the case in settings where resources are limited, where programmes are more likely to use methods such as clinical breast examination.

These data provides us with information on the number of countries with policies relating to NCDs, obesity, alcohol and physical activity, and this is likely to have some impact on breast cancer prevention as they address common risk factors. We were also able to assess the global availability of breast screening policies, which indicate that this is widely practiced globally. The next section examines the extent to which breast cancer is addressed as part of such policy documents in the context of three countries. We also examine breast cancer specific policies in these countries such as those relating to specific health promotion activities (e.g. breast awareness), screening programmes and the care pathway for those at high risk due to genetic susceptibility or family history.

Figure 1 *Global overview of prevention policies impacting on breast cancer prevention.*
Source: [World Health organisation Data for 2015]



Case study 1: The United Kingdom

Who is involved in breast cancer prevention?

Healthcare within the United Kingdom is publicly funded and delivered by different systems in each devolved nation - NHS England, NHS Scotland, NHS Wales and Health and Social Care in Northern Ireland. National healthcare spending is decided by the UK central government, which allocates resources to each of the four nations according to population size.

Healthcare in each nation is managed by their respective governments and health systems, which has resulted in disparities in healthcare provision across the UK. Each national government has a department dedicated to health, which oversees policy and resource allocation to non-departmental public bodies such as the NHS [56, 57, 58, 59].

Delivery of NHS services is managed by Clinical Commissioning Groups (CCGs) in England, local Health Boards in Scotland and Wales, and Health and Social Care Trusts in Northern Ireland.

National healthcare policy is supported by specialist public bodies, such as the National Institute for Health and Care Excellence (NICE) and public health organisations such as Public Health England (PHE) and Health Protection Scotland.

NICE develop clinical care guidelines with input from each of the devolved nations. These apply primarily to England but may be adopted by the other nations at the discretion of their administrations.

Public health organisations in each country produce health promotion guidance and deliver public health programmes of relevance to, but not specifically designed for, breast cancer prevention [60, 61, 62, 63].

Devising and implementing policy recommendations for health promotion interventions involves numerous organisations within the UK and in each of its devolved governments. Although no strategies exist specifically for the primary prevention of breast cancer in the general population, policy development and delivery measures are in place to address a number of modifiable risk factors associated with breast cancer: physical activity, obesity, tobacco and alcohol consumption and breastfeeding.

Each devolved government has set out desired outcomes and indicators (e.g. breastfeeding, excess weight in adults, smoking prevalence etc.) that allow assessment of achieving policy goals.

Cancer screening guidelines for the entirety of the UK are determined by a UK National Screening Committee [64]. Healthcare strategy may also be influenced by contributions and the work of external non-governmental organisations (NGOs).

Major NGOs involved in making evidence-based policy recommendations include Cancer Research UK, Cancer Support and the World Cancer Research Fund UK.

Policy analysis

Physical activity

The Chief Medical Officers from each devolved nation have collaboratively published UK-wide physical activity guidelines for all age groups. The report which contributed to these guidelines refers to the potential reduction in breast cancer risk through engaging in physical activity [65]. Frameworks have been formulated in each country at central and local government levels for the implementation of these guidelines to reduce the risk of cancer and chronic disease, but make very limited specific reference to breast cancer [66, 67, 68, 69]. National guidance is available from NICE on encouraging physical activity and healthy dietary habits in all age groups, for the purposes of preventing excess weight gain and reducing risk of associated diseases including cancer [70]. Service delivery programmes are in place in each of the devolved nations to encourage children and adults to participate in physical activity [71, 72, 73, 74].

Obesity

Each devolved government has established action plans and mechanisms to prevent and treat obesity, through promoting physical activity and improving nutrition [66, 71, 76, 74]. These include frameworks, service planning measures and publicly accessible programmes for adults and children such as Change4Life. The objectives of these initiatives are broadly to encourage weight loss among individuals who are already overweight or obese, and to prevent obesity through education regarding healthy dietary choices. Reference is made to the role of obesity in increasing cancer risk, and specifically to breast cancer in the publications by the Scottish and Northern Irish governments. Clinical guidelines for obesity prevention and management have also been published by NICE [70, 77, 78].

Alcohol and tobacco

Most policy relating to alcohol and tobacco acknowledge their contribution to increased risk of cancers but, owing to the wide range of disease associations, their impact specifically on breast cancer risk is not thoroughly described. The Chief Medical Officers from each devolved nation collaboratively published UK-wide weekly drinking guidelines, which refer to the risk of cancers including of the breast [79]. The major goal of such policies is to reduce exposure in order to reduce the burden of diseases related to these substances.

A key policy in the UK alcohol strategy is to support individuals to change behaviour through a better understanding of the risks of alcohol. One mechanism identified to achieve this is through improving public health information. A report published by Cancer Research UK examining public attitudes towards alcohol policy identified that, although alcohol was acknowledged as a risk factor for cancer, levels of knowledge with regards to its impact on breast cancer were low [80].

Breastfeeding

Increasing breastfeeding is highlighted in many government policy documents due to its impact on child and maternal health, and it is one of the specific indicators used by each of the devolved nations to measure health outcomes. Although the emphasis of breastfeeding in these documents is from a child health perspective, they do acknowledge the benefits for maternal health including reducing risk of breast cancer. NICE guidance in a number of areas such as antenatal and postnatal care also refer to the benefits of breast feeding for reducing risk of breast cancer. NICE also recommend that women presenting to a healthcare professional with concerns about familial breast cancer should be advised to breastfeed where possible, as a risk-reduction strategy [81].

Cancer

Cancer strategies have been produced by each of the devolved governments. They have in common recommendations relating to tobacco, alcohol, obesity and overweight, physical activity and healthy eating to reduce the incidence of cancer. In addition the cancer strategy for England acknowledges the increased need for personalised prevention through mechanisms such as stratified screening, risk-based prevention and surveillance programmes.

None of these documents have recommendations specific to primary prevention of breast cancer. However, the Scottish Government document *Beating Cancer: Ambition and Action* outlines that the Scottish government will explore 'how initiatives like the 'Act Well' programme, (a personalised breast cancer risk reduction programme offered to women attending routine breast screening clinics) can be fully tested for effectiveness and roll out.'

In summary, although policy documents recognise risk factors contributing to breast cancer, there are few specific actions in relation to primary prevention, other than reduction in alcohol, tobacco and obesity. Furthermore the policy messages relating to these risk factors are general and not breast cancer specific. This is unsurprising given the wide range of impact these risk factors have and the balance that must be achieved between providing meaningful information that is not complicated by excessive detail.

The prevention pathway

Health promotion

Strategies for the primary prevention of breast cancer among the general population predominantly involve dissemination of lifestyle advice aimed at reducing modifiable risk factors. Lifestyle advice is made freely available to the public by major cancer and breast cancer charities, through printed and online resources. Specific and accessible information on breast cancer and genetic testing is also provided through the NHS Choices website. In addition, NICE advocate that healthcare professionals carefully consider the relative risks and benefits of hormonal therapy in women aged over 35, encourage breastfeeding, and promote adoption of healthy lifestyle choices with regards to alcohol consumption, smoking, weight and physical activity in line with national guidelines [81].

Population screening

An organised screening programme is in place and offered to all women between the ages of 50-70. As the programme does not take into consideration other risk factors apart from age, women are not further stratified to identify those who may be at different levels of risk. Eligible women are invited to participate in routine screening mammography, on a three-yearly basis through the NHS Breast Cancer Screening Programme [82]. Women above the age of 70 are eligible for further triennial mammography upon request, and account for the majority of referrals to the programme by individuals or through primary care practitioners [82, 83]. The cluster-randomised AgeX trial involving approximately 85% of UK breast screening units is currently underway to investigate the potential benefits of extending routine radiographic breast imaging to women aged 47-73, and in some units up to age 79, which is expected to be concluded in 2027 [84]. Partly as a result of this extension to the eligible age range for screening mammography, around 2,300 additional breast malignancies were identified in 2014-15 than in 2004-05 among women aged 45-49 and over age 70 [83].

Guidelines are in place for enhanced surveillance of women at moderate or high risk due to family history or exposure to supradiaphragmatic radiotherapy before age 30, or with known genetic susceptibility to breast cancer. These women undergo screening using both mammography and magnetic resonance imaging (MRI). However, there is no systematic programme in the UK for identifying women in the general population eligible for enhanced screening.

The second Predicting Risk of Cancer At Screening (PROCAS) study is underway to assess the potential benefit of calculating breast cancer risk based upon family history and modifiable risk factors among women attending their first screening mammography, and whether communicating this information encourages positive lifestyle modification.

Identification of women at high risk due to family history or genetic susceptibility

General Practitioners are advised not to actively seek women with a positive family history of breast cancer in most instances. This information is only collected for women aged over 35 who are using or considering using the combined oral contraceptive pill (COCP) or hormone replacement therapy (HRT) [81]. Despite calls for this approach to be reviewed this guideline has remained in place since 2004 with no clear rationale outlined in NICE supporting evidence documents [85]. As such, in the absence of routine assessment of family history, identifying the majority of women at moderate to high risk of breast cancer due to genetic factors is dependent upon awareness by the individual of a significant family history and their subsequent presentation to a primary care practitioner.

NICE indicate that all individuals who present to a medical practitioner with concerns about familial breast cancer should be issued with standard written information regarding breast awareness, disease risk factors and recommendations for lifestyle modification. NICE recommend that this information should follow a standard structure, but it is the responsibility of medical practitioners to compose their own 'standard information' which both reflects evidence-based national guidelines and is tailored to the individual patient, taking their level of risk into account to enable targeted risk reduction strategies to be devised.

Assessment of high risk individuals due to family history or genetic susceptibility

Depending on the specific family history criteria met (as defined by NICE) at the primary care level, an individual may be referred for further assessment in a secondary or tertiary care setting. Further risk assessment is undertaken, during which *BRCA1/2* gene mutation carrier probability can be estimated using carrier prediction algorithms such as BOADICEA or the Manchester scoring system [46, 81, 85]. Both prediction models take into account the occurrence and age at presentation of cancers of the breast, ovaries, pancreas and prostate among first, second and third degree relatives [46, 87, 88]. Those with an estimated gene mutation probability of 10% or higher, or a high lifetime breast cancer risk of 30% or greater, are offered the opportunity of referral to a tertiary care specialist genetic clinic where genetic testing for *BRCA1/2* and *TP53* mutations may be performed following adequate genetic counselling [81].

The most recent update of the BOADICEA model also provides risk estimates for *PALB2*, *CHEK2* and *ATM*, which accumulating evidence suggests are also associated with a clinically important increased risk of breast cancer [89, 90]. No mention of these is made in NICE guidelines, which has led to regional variation in service provision for genetic testing and in the gene panels that are used. Women with a moderate lifetime breast cancer risk of between 17% and 30% may be referred for annual mammography from age 40 after assessment in a secondary care setting [81, 91].

Women for whom genetic susceptibility to developing breast cancer has been established may be eligible for chemoprevention or risk-reducing bilateral mastectomy and/or oophorectomy as primary preventative measures. Women at high risk of breast cancer, with a known or probable (>30%) *BRCA1/2* mutation, may be offered annual screening by dual MRI and mammography from the age of 30 [81, 91].

Summary

The principal approaches to primary prevention of breast cancer in the UK are to inform and empower individuals to reduce their own risk of breast cancer through health promotion. Established screening programmes allow early detection and provision of appropriate treatment to individuals. Health promotion messages are not targeted at specific at-risk groups or modulated to address those with differing risk factors. Although there is provision of preventative measures to those at high risk due to a family history or genetic susceptibility, there is no systematic approach for the identification of these individuals. Furthermore, pathways of care are most well established for those who are considered to be high risk due to possessing *BRCA1/2* mutations.

Case Study 2: The Netherlands

Who is involved in breast cancer prevention?

Residents of the Netherlands are legally obliged under the Health Insurance Act to purchase a standard health insurance package to cover the costs of consultations, hospital treatment and prescription medication, costing each individual around €1,200 per year. Those on low incomes may be eligible for healthcare benefit, to assist with insurance costs. Using recommendations from the National Health Care Institute (ZIN), the Ministry of Health, Welfare and Sport (VWS) decides the content of the basic health insurance package and is indirectly involved in its implementation, which is primarily organised by the health insurers themselves. Quality assurance of the healthcare services provided is overseen by the Dutch Healthcare Inspectorate (IGZ) [92, 93].

National healthcare policy is determined by the Ministry of Health, Welfare and Sport, with support from independent advisory bodies such as the National Health Care Institute, the Health Council of the Netherlands, and the National Institute for Public Health and the Environment (RIVM) which utilises public health research to formulate evidence-based policy.

The Public Health Department (PG) within the Ministry of Health, Welfare and Sport supports local health policy development in municipalities and the National Population Screening Programmes coordinated by the Centre for Population Screening at RIVM [92, 93].

Health policy is also influenced by NGOs such as World Cancer Research Fund Netherlands and the Dutch Cancer Society (KWF), which funds scientific research and provides health promotion materials for many types of cancer [94, 95].

There are no specific strategies in place for the primary prevention of breast cancer within the general population, but policies have been developed to address the major modifiable risk factors associated with breast cancer.

Policy analysis

The government's health policy is set out in a national health policy document that is updated every four years. The most recent available document is *Health Close to People* which sets out policy for 2011-2015. This document places emphasis on addressing overweight and obesity, smoking, excessive alcohol consumption and improving physical activity [96]. These policy goals were supported by the National Programme for Prevention (NPP) launched in 2014. This is a joint effort by six ministries, municipalities, businesses and civil society organisations and encompasses a wide range of activities. They include initiatives such as ensuring the availability of sports facilities close to people's homes and education in schools. Physical activity guidelines have also been produced by the government.

Obesity

Reducing obesity is one of the priorities set out in the National Programme for Prevention. Government-funded initiatives such as the Sports and Moving in the Neighbourhood Programme improve the accessibility of sports coaching and activities within local areas [97]. The Nutrition Centre is a publicly funded online resource which provides educational material on healthy diet and nutrition choices for individuals who want to lose weight [98]. Programmes specifically aimed at children and adolescents are also in place, to improve both dietary options in schools and to encourage engagement in physical activity [99, 100].

Alcohol and tobacco

Alcohol policy is mainly aimed at responsible drinking, minimising addiction and consequences of alcohol abuse. There is a particular focus on educating young people of the risks of alcohol abuse and dependence, and to reduce the incidence of alcohol consumption in adolescence. Similarly, tobacco policy concentrates on reducing number of smokers, prevention of uptake of smoking and assisting people to quit smoking. Restrictions are in place on advertising and smoking in public places, and concentrated efforts are being made to educate young people on the harms of smoking and to provide support to those who wish to stop.

Breastfeeding

Breastfeeding is advocated by the Ministry of Health, Welfare and Sport. Most hospitals in the Netherlands adhere to the Unicef Baby Friendly initiative, which outlines steps to support new mothers in breastfeeding [101, 102]. In addition, the Nutrition Centre provides online educational material for breastfeeding and its advantages for mothers and babies, and makes specific reference to the reduced risk of breast cancer [103].

Cancer

Cancer prevention strategies in the Netherlands have been outlined in the National Cancer Control Programme (NPK), which was devised by five organisations including the Ministry of Health, Welfare and Sport, and the Dutch Cancer Society. The most recent available documents relate to the programme for 2005-2010, and cover all aspects of cancer control including prevention, screening, diagnosis, treatment and aftercare.

Among the strategies for primary prevention, reducing the number of smokers was a particular focus, but actions for increasing awareness of risk factors and early symptoms of cancer among the general public, in addition to tackling obesity and alcohol consumption, were also devised. Physical inactivity and alcohol were specified as particular risk factors for breast cancer development [104, 105].

Current practice

Health promotion

The most recent available National Programme for Prevention and *Health Close to People* policy documents focus on the need to address alcohol consumption, smoking, diabetes, overweight and physical inactivity for the prevention of chronic disease and promotion of health, but make no specific reference to breast cancer [96, 105].

As part of the National Cancer Control Programme, a national campaign entitled "Six times stronger against cancer" was run to improve public awareness of risk factors for cancer, particularly focussing on beneficial lifestyle modifications. The Dutch Cancer Society also ran a national campaign entitled 'Knowing the nine signs' to improve the early self-detection of cancer [105].

The Dutch College of General Practitioners (NHG) provide guidelines on the investigation and management of obesity, and approaches to addressing smoking and alcohol abuse, but make little specific mention of cancer risk [106, 107, 108].

Population screening

The national breast cancer screening programme is managed by the RIVM Centre for Population Screening (CvB) on behalf of the Ministry of Health, Welfare and Sports and is delivered by five regional screening organisations. Quality of delivery of the programme is assessed by an independent body, the Dutch Expert Centre for Screening (LRCB). All women between the ages of 50-75 are invited to attend routine screening mammography on a biennial basis, and approximately 80% of women participate in the programme [109]. Breast cancer screening is not performed above the age of 75.

Enhanced surveillance is recommended for women at moderate or high risk of breast cancer due to exposure to thoracic radiotherapy before age 40, long-term HRT use, their family history, and those who carry high penetrance genetic mutations including *BRCA1/2*. Women with a very high cumulative life time risk (CLTR) of 60-80%, due to confirmed *BRCA1/2* mutations or a mutation carrier probability of at least 50%, are eligible to receive annual breast examination and MRI screening from age 25 to age 60, and additional annual mammography from age 30 until age 75.

Those with a high CLTR of 30-40% due to family history should be offered annual mammography and clinical breast examination between ages 35-60 and should resume routine mammographic screening thereafter. Women at a moderately increased CLTR of 20-30%, due to family history or long-term HRT use for 10 years or more, are eligible for enhanced screening mammography from the age of 40 at the request of their General Practitioner, followed by routine mammography from age 50 [110].

There is no systematic programme for identifying women eligible for enhanced screening, but the ongoing PRISMA study is currently underway to assess the potential impact of personalised risk-based screening using participant data relating to risk factors, biomarkers and mammographic results [111]. The benefits of biennial MRI screening in addition to routine mammography are also being investigated for women with extremely dense breast tissue in the ongoing DENSE trial [112, 113].

Identification of women at high risk due to family history or genetic susceptibility

Guidelines set by the Dutch College of General Practitioners suggest that it may be opportune to seek family history information from individuals at the time of their registration to a medical practice. No explicit recommendations are given by NHG to routinely enquire about family history of breast cancer during consultations, except where women are considering using the COCP or HRT [114, 115, 116].

As such, unless women are prompted to provide information regarding family history of breast cancer when changing their primary care provider or commencing hormonal therapy, women in the general population take primary responsibility for approaching their General Practitioner with concerns about their breast cancer risk. In women without known genetic mutations, guidelines have been set out using family history criteria to categorise them according to their relative risk of breast cancer development.

Assessment of high risk individuals due to family history or genetic susceptibility

General Practitioners are able to refer individuals who meet defined criteria suggestive of familial breast cancer directly to specialist genetic clinics [109, 117]. A freely available online tool has been developed to aid identification of women at high familial breast cancer risk by healthcare professionals or through self-testing, which was recently evaluated in a small study to identify women at moderate or high risk without inducing anxiety [118, 119]. Clinical geneticists calculate *BRCA1/2* gene mutation carrier probability predominantly using the Claus model, but algorithms such as BOADICEA are also advocated [117].

Lifetime risk of breast cancer may also be calculated using the Claus or Claus-Extended model [120]. Genetic testing is offered to individuals with an estimated *BRCA1/2* mutation probability of 10% or higher, and should incorporate broader testing for hereditary cancer syndromes, such as Li-Fraumeni syndrome caused by mutations in *TP53* and *CHEK2* [110].

Updated clinical guidelines set by the Foundation for the Detection of Hereditary Tumours (StOET) distinguish between familial breast cancer, defined in this guideline as a familial trait of undetermined genetic origin, and hereditary breast cancers, caused by mutations in *BRCA1/2*, T*P53, PTEN* and *CHEK2* genes. The guideline specifies differential measures for the prevention, diagnosis and management of familial and hereditary breast tumours, predetermined by each genetic mutation, in clinical practice.

Individuals who are confirmed *BRCA1/2* mutation carriers are eligible for prophylactic bilateral mastectomy and/or oophorectomy, and should be counselled regarding the use of the COCP which further increases the risk of breast cancer but is beneficial for ovarian cancer risk reduction [117]. Once the mutation has been characterised, predictive testing can be offered to healthy relatives of the affected individual upon reaching early adulthood [121]. Those with a familial trait are offered enhanced screening.

Summary

As in the UK, breast cancer prevention strategies are most well defined for individuals at increased risk due to family history or genetic susceptibility, but no measures are in place for the systematic identification of these individuals within the general population.

A national mammographic screening programme is in place to facilitate the earlier detection and treatment of breast cancer among women within the eligible age range of 50-75 years. Clinical pathways for management of individuals with very high risk *BRCA1/2* mutations or hereditary cancer syndromes have been established, and national guidelines recommending testing for gene mutations other than *BRCA1/2* suggest that there may be less regional variation in service provision for genetic testing in clinical practice.

Case study 3: Australia

Who is involved in breast cancer prevention?

Public healthcare in Australia is funded from taxpayer contributions through the universal public health insurance scheme Medicare. Contributions are means-tested, with rebates available for those on low incomes and additional surcharges for those on high incomes. Financial incentives are provided by the Australian Government for taking out private health insurance, including subsidies on a means-tested basis and waivers of surcharges. The governments of each state or territory manage public sector health services and regulate private healthcare providers [122, 123]. Health policy is decided on a national level by the Council of Australian Governments (COAG) Health Council, which involves the Ministers for Health from the central, state and territory governments. Health policy development is supported by the federal Department of Health and the Australian Health Ministers' Advisory Council (AHMAC) [124].

Cancer Australia is a central governmental cancer control agency that contributes to development of cancer-specific policy and strategy.

NGOs such as Cancer Council Australia also advise the governments on cancer strategies, and the Public Health Association of Australia provides policy research support relating to health promotion and disease prevention activities. BreastScreen Australia is the national breast cancer screening programme, coordinated as a joint initiative of central, state and territory governments.

Policy implementation and service delivery of public healthcare and cancer screening programmes are the responsibility of the individual governments of each state or territory [122].

Policy analysis

Physical activity

The Australian Government Preventative Health Taskforce highlights increasing physical activity as an important approach to reducing obesity and, in turn, decreasing cancer risk [125]. National Physical Activity and Sedentary Behaviour Guidelines for adults advise that at least moderate-intensity physical activity is beneficial in general cancer prevention [126]. Clinical guidelines by the Royal Australian College of General Practitioners recommend that primary care practitioners identify individuals at high risk of cancer, and offer interventions such as prescribed exercise programmes to encourage participation in physical activity [127].

Obesity

The Australian Government Preventative Health Taskforce has set out a national strategy on obesity prevention. Whilst reference is made to obesity as a risk factor for multiple types of cancer, including breast cancer, no specific information is provided regarding approaches to prevention and management of obesity in the context of breast cancer [125].

Alcohol and tobacco

National strategies for encouraging avoidance of tobacco use and excessive consumption of alcohol are outlined in the National Preventative Health Strategy document, authored by the National Preventative Health Taskforce. With the exception of lung cancer, no reference is made to the role of alcohol and tobacco as risk factors for cancer [125].

The National Tobacco Strategy for the period 2012-18 outlines approaches for reducing the prevalence of smoking [128]. National guidelines on reducing health risks from alcohol consumption cite breast cancer as a potential adverse effect of alcohol, but offer no specific health promotion advice in this regard [129].

Cancer

The strategic plan set out by Cancer Australia outlines their commitment to reducing cancer incidence through improvements in prevention, screening, diagnosis and treatment [130]. Their position statement on primary prevention of cancer makes clear recommendations on beneficial lifestyle modifications relating to tobacco, weight, physical activity and alcohol consumption, and provides evidence for positive associations between these factors and development of breast cancer [131].

Breastfeeding

The National Preventative Health Taskforce advocate breastfeeding for the purposes of child nutrition and future health, but no mention is made of the protective benefits of breastfeeding against breast cancer [125]. The National Breastfeeding Strategy endorsed by the Department of Health makes a single reference to the reduction in risk of breast and ovarian cancer from breastfeeding [132].

The prevention pathway

Health promotion

The Royal Australian College of General Practitioners has published clinical *Guidelines for preventive activities in general practice*, which provides evidence-based advice to General Practitioners on reducing risk of chronic diseases and cancer, including breast cancer specifically, in primary care settings. These include general recommendations on physical activity, diet, weight and alcohol consumption, which it is suggested should be approached during consultations with individual patients every two years [127].

More extensive information is available online through Cancer Australia, which publishes breast cancer-specific clinical guidelines for healthcare professionals and informative, accessible patient resources, such as a user-friendly breast cancer risk calculator based on family history and lifestyle choices [133, 134].

Population screening

Biennial screening mammography is routinely offered to all women between the ages of 50-74. Women between the ages of 40-49 and over the age of 74 are able to self-refer for free biennial screening mammography through their General Practitioner, without requiring an invitation or a clinical indication for additional surveillance [133]. General Practitioners should discuss the relative benefits and harms of undergoing additional screening to allow an informed decision to be reached by the individual [127].

Enhanced screening in the form of annual screening mammography is offered from age 40 to women who have a first degree relative diagnosed with breast cancer before age 50. Access to MRI screening through Medicare is restricted to asymptomatic women under age 50 at high risk of breast cancer (>3 times population risk), as a result of known genetic susceptibility or particular family history criteria suggestive of familial breast cancer [135, 136].

Identification of women at high risk due to family history or genetic susceptibility

The Royal Australian College of General Practitioners recommend that a comprehensive family history should be taken from every patient in primary care and regularly updated. A family history questionnaire is provided in their guidelines which is suitable for use at the time of new patient registration [127]. General Practitioners should also counsel women on the risks and benefits of HRT in the context of family history, and review the continuing need for hormonal therapy on a six to twelve monthly basis [137].

An online Familial Risk Assessment – Breast and Ovarian Cancer (FRA-BOC) tool is available from Cancer Australia to facilitate the assessment of women presenting to their General Practitioner with concerns about familial breast and ovarian cancer. This tool provides risk estimates relative to the general population, which form the basis of three categories of risk ('average', 'moderately increased', and 'potentially high'). In all cases, women should be informed of the modifiable risk factors for breast cancer and encouraged to practice breast awareness [138]. General Practitioners make direct referrals to family cancer clinics for women at high risk of breast cancer, and should offer the opportunity for referral to women at moderate risk (1.5 to 3 times population risk) [138]. However, family history collection is still largely opportunistic.

Assessment of high risk individuals due to family history or genetic susceptibility

Extensive risk assessment and management of women at moderate and high risk of breast cancer is provided in family cancer clinics. Genetic testing for *BRCA1/2* and other mutations is available to women with an estimated mutation probability of 10% or higher, calculated using algorithms such as BOADICEA[139]. Extensive clinical guidelines relating to testing criteria and risk management for other genetic mutations relevant to breast cancer, including TP53, PTEN and ATM, are also available from the online eviQ resource for cancer treatment protocols [140]. If a mutation is identified in these genes, predictive genetic testing is subsequently offered to family members [141]. Since November 2017, this testing has is covered by a Medicare rebate leading to wider access and potentially increased testing in Australia.

Women at high risk of developing breast cancer, regardless of their genetic susceptibility, are eligible for annual breast imaging by mammography, MRI or ultrasound [136]. Clinical guidelines state that women with confirmed *BRCA1/2* gene mutations should receive annual screening by mammography and MRI from age 30, and by annual mammography alone from age 50 [142, 143]. Risk reduction strategies such as chemoprevention and surgery should also be discussed with women with confirmed *BRCA1/2* mutations. Chemoprevention may also be considered in women at moderate risk over age 35, after thorough evaluation of the relative risks and benefits of therapy [132].

Summary

As in the UK and Netherlands, a national screening programme is available in Australia to women within the general population, which is routinely offered to women within the age range of 50-74 years. Extensive health promotion guidance relating to cancer risk is available for primary care practitioners, and is communicated in an accessible format to the public through Cancer Australia. Unlike the UK, but similar to the Netherlands, General Practitioners are able to categorise women according to their breast cancer risk and refer them directly to specialist genetics clinics. The approaches to management of women at increased risk are similar across all countries, and predominantly involve enhanced surveillance for those at greater risk and risk-reducing measures, such as chemoprevention and prophylactic surgery.

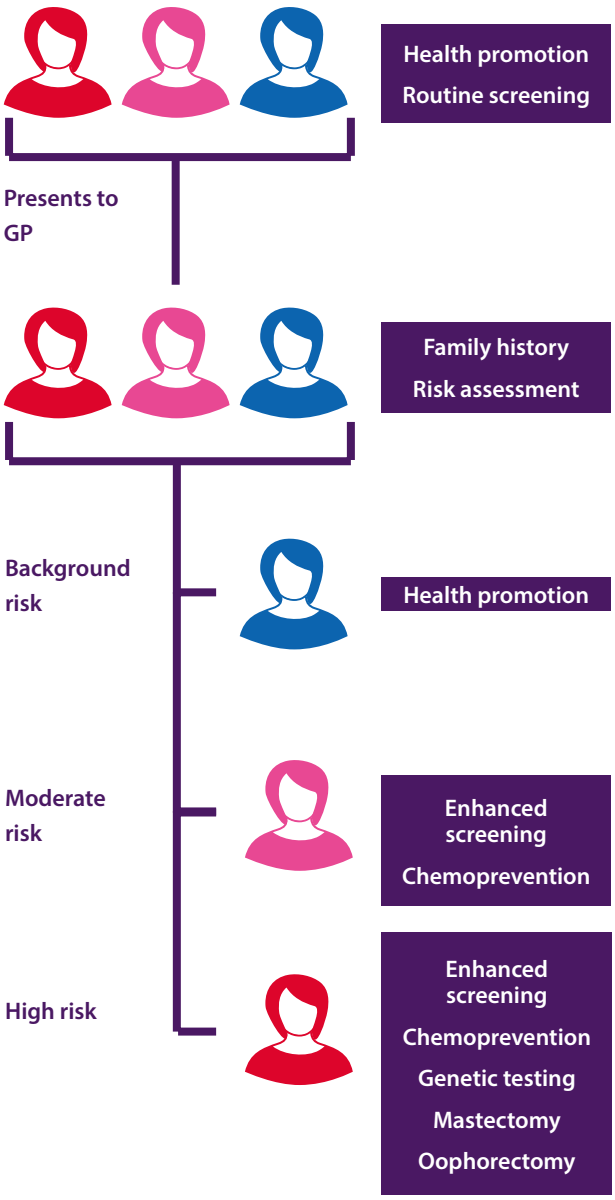
4.4 Summary of the breast cancer policy landscape

Examination of the global and national policy landscape indicate that there is recognition that breast cancer is an important cause of mortality and morbidity [52] and improving primary prevention is a goal of many policy makers. The main approach to prevention is through health promotion to inform and empower individuals to reduce their own risk. However, these messages are not targeted at specific at-risk groups or modulated in any way. Furthermore, policy documents aimed at general risk factors often do not identify breast cancer as an important disease for which risk could be reduced. Established screening programmes enable early detection and treatment on a population-wide scale. Although preventative strategies are available for those at high/moderate risk as a result of genetic factors or family history, identification of these women is opportunistic.

In most countries pathways of care are most well established for those who are considered high risk due to possessing *BRCA1/2* mutations, which are summarised in Figure 2.

Table 5 summarises the policy landscape for health promotion activities in each country studied.

Figure 2 The prevention pathway



UK	Netherlands	Australia
Breast awareness, lifestyle modification		
Triennial Ages 50-70	Biennial Ages 50-75	Biennial Ages 50-74
GP referral to secondary care	GP referral to tertiary care	GP referral to tertiary care
Breast awareness, lifestyle modification		
Annual mammography from age 40		
Annual MRI/mammography		
Age 30+	Age 25/30+	Age 30+
>10% *BRCA1/2* mutation probability		

Table 5 Summary of the health promotion policy landscape in the UK, the Netherlands and Australia

Policy area	UK	Netherlands	Australia
Physical activity	Physical activity encouraged in CMO report to reduce breast cancer risk [65], but very limited reference to breast cancer in national and local government frameworks.	Policy to improve physical activity outlined in *Health Close to People* and supported by the National Programme for Prevention [84, 96]. No specific reference to breast cancer is made.	Importance of physical activity for cancer prevention is outlined by the national Preventative Health Taskforce [126], but no specific reference to breast cancer is made.
Obesity	Frameworks, clinical guidelines and service planning measures in place to address obesity. Specific reference to breast cancer risk by Scottish and Northern Irish governments.	Policy to address obesity outlined in *Health Close to People* and supported by the National Programme for Prevention [97, 98, 99, 100]. No specific reference to breast cancer is made.	Reference is made to the importance of obesity as a risk factor for cancer by the national Preventative Health Taskforce, but not specifically for breast cancer [125].
Alcohol and tobacco	Weekly drinking limits recommended to reduce cancer risk, including of the breast, in CMO report [79].	No specific reference to breast cancer is made. Policy for reducing alcohol consumption and smoking outlined in "Health Close to People" and supported by the National Programme for Prevention [96].	National guidelines cite breast cancer as a potential adverse effect of alcohol, but offer no health promotion advice [128]. Tobacco use is only considered in the context of lung cancer [129].
Breastfeeding	NICE recommend breastfeeding as a breast cancer risk-reduction strategy, especially among those concerned about familial cancer risk [81].	Breastfeeding recommended by the government. Publicly funded online resource makes reference to breast cancer risk reduction [103].	The National Breastfeeding Strategy encourages breastfeeding, and cites the benefits for reducing risk of breast and ovarian cancers [132].
Cancer	No specific reference to breast cancer made in cancer strategies, but all share recommendations for tobacco, alcohol, obesity, physical activity and diet. Cancer strategy for England advocates personalised prevention programmes. Scottish government are exploring effectiveness of personalised breast cancer risk reduction programme.	Strategies relating to prevention, screening, diagnosis, treatment and post-treatment care are outlined in the National Cancer Control Programme. Reducing smoking, alcohol consumption and obesity are important areas for primary prevention. Physical inactivity and alcohol are specified as particular risk factors for breast cancer [104, 105].	Strategic plan by Cancer Australia outlines their commitment to improving prevention, screening, diagnosis and treatment [58]. They make clear recommendations on beneficial lifestyle modifications relating to tobacco, weight, physical activity and alcohol consumption, for breast cancer risk reduction [130].

5. Opportunities for increased personalisation of breast cancer prevention

Key points:

- Personalised healthcare is recognised as an important area of policy development
- Personalised prevention is an area of discourse for public health and policy to some extent, with much of the dialogue centred around the contribution of genomics
- Much of the discussion surrounding personalised prevention is in the context of stratified screening or treatment stratification
- There is an absence of a clear vision and strategy for development of personalised prevention for breast cancer

5.1 Personalised prevention

Personalisation of medicine is not a new concept but is an evolving process that aims to continually improve the effectiveness and efficiency of medical practice. One way this can be achieved is by better understanding how the unique biological characteristics of individuals and their social/environmental contexts contribute to their health and disease. Scientific and technological advances have facilitated this process through the identification of novel biomarkers that can be used to better differentiate between individuals, thereby increasing the extent to which we can characterise them and develop a wider choice of interventions. Such advances are enabling increased personalised prevention, which we can define as the combination of better differentiation between individuals based on biological characteristics and the offer of tailored interventions. This allows a move away from the 'one size fits all' approach to one that seeks to determine individual risk and provide appropriate interventions on the basis of this risk. Achieving this requires both appropriate tools to identify those at different levels of risk and the availability of different strategies of care for these individuals.

In this section we first describe technological and scientific advances that are creating opportunities for increased personalisation of breast cancer prevention. We have only included technologies that are contributing to primary prevention and early detection of breast cancer. We also provide the results of our examination of the discourse and debate surrounding personalised prevention among policy makers and public health practitioners.

5.2 What is enabling the provision of personalised prevention?

Shifting technological landscape

Technological advances in a number of areas are contributing to our ability to enable more personalised prevention. This ranges from technologies that are allowing more precise and wider characterisation of disease biomarkers as well as those supporting technologies that are allowing care to be delivered in novel ways. The development of multiplex technologies that facillitate assessment of multiple biomarkers has contributed to a step change in the number of disease associated biomarkers that can be assessed at one time. Progress in the development of wearable and digital technologies are also enabling data collection on a number of characteristics in a more accessible manner. Advances in computing are enabling this information to be bought together and assessed more comprehensively. The development of Apps and Smart devices is also changing the way communication between individual citizens and health system takes place. They are opening new avenues to explore how healthcare can be delivered and are creating greater diversity in provision of health information.

Biomarker discovery

Apart from genes there are no other endogenous biomarkers that we currently know of that can be used in biological characterisation of individuals in assessing their breast cancer risk. Still, genetic information can enable identification of those individuals who are at high risk due to mutations in genes such as *BRCA1/2*. In individuals who do not possess these high risk variants, combinations of single genetic variants still contribute to risk. However, the impact of these variants needs to be considered against a background of other biological and environmental risk factors. Attempts are being made to identify novel genes contributing to breast cancer risk [144] and genetic modifiers of risk in those carrying mutations in *BRCA1/2* genes. However, wider testing to determine possession of high risk genes apart from *BRCA1/2* or SNPs that increase risk is still an area of debate.

Our understanding of proteomics, metabolomics and epigenetics has progressed and these fields are contributing to breast cancer risk assessment, however, this is in those who have already developed disease. Examples include gene expression arrays which provide information on prognosis of breast cancer as well as likelihood of response to radio- and chemotherapy.

Early detection of breast cancer currently relies mostly on mammography and although attempts are being made to identify blood-borne tumour markers, this field is still at an early stage. Another area of development is the analysis of breath volatile organic compounds (VOCs). These are compounds whose levels increase as a result of the disease process. Attempts are being made to develop point-of-care devices that enable analysis of these compounds for early disease detection [145].

Continuous monitoring

Attempts are also being made to develop devices that enable monitoring by individuals in their homes. These include the development of a smart bra – ITBra by Cycardia Health. This comprises wearable sensors that collect information on circadian temperature changes within breast tissue. The data are analysed by algorithms to identify and categorise abnormal patterns and the user is notified if there are concerns. Initial clinical studies of this device have been completed and additional clinical trials are underway. Other companies include Celestia Health and iSonoHealth who have developed wearable technologies that enable users to assess changes in breast health. Apps that are part of these devices enable sharing of information with health professionals.

Enabling diversity in care pathways

With more widespread use of mobile phone technology, mHealth interventions such as Apps (e.g. to disseminate information) and text messages (e.g. to remind patients to attend screening) are beginning to be effective ways of engaging individuals and providing healthcare (such as via telemedicine). There are a wide range of Apps available providing educational information or trying to encourage behaviour change. The combination of diverse means of communication, information presentation and means of achieving health goals creates the possibility of providing different options that are suitable for different sub-populations.

Risk prediction algorithms

As discussed in the previous section, algorithms to predict risk of breast cancer have already been developed, however, their current use is within a limited scope. Current models either predict risk of carrying a high risk genetic mutation or the risk of developing breast cancer with or without possession of mutations. Consequently they are more useful in settings where family history is known. Their application to different care settings, which inevitably encompass different population groups, requires further consideration.

5.3 Grey literature search strategy

We carried out a review of the grey literature in the context of three countries (UK, Australia and Netherlands) with the aim of investigating the inclusion of personalised breast cancer prevention within the discourse of public health and policy makers. Our objective was to examine how personalised prevention and specifically personalised prevention of breast cancer is viewed by different stakeholders involved in developing or influencing policy in this area. This included government, public health organisations, clinicians through clinical societies and key independent bodies that can influence policy in this area.

We endeavoured to identify policy documents, blogs or commentaries published by these stakeholders and analysed them to identify the extent to which personalised prevention was included in these publications, the context and the main focus areas. It was anticipated that the literature in this area would be limited and it is likely that personalised prevention would be included within the wider context of personalised healthcare; therefore the search strategy was intended to be sensitive rather than specific. Data sources to be searched were identified through consultation with experts to ensure they covered the relevant stakeholder groups. The data sources are in the Appendix (Table 1) along with the search terms, inclusion and exclusion criteria. We restricted our search to the time period 2012-2017, in order to focus on the current discourse. However, we did consult with experts to attempt to identify key documents published prior to this time period in order to allow us to provide a historical context. Searches were conducted between June and July 2017.

5.4 Personalised prevention – UK

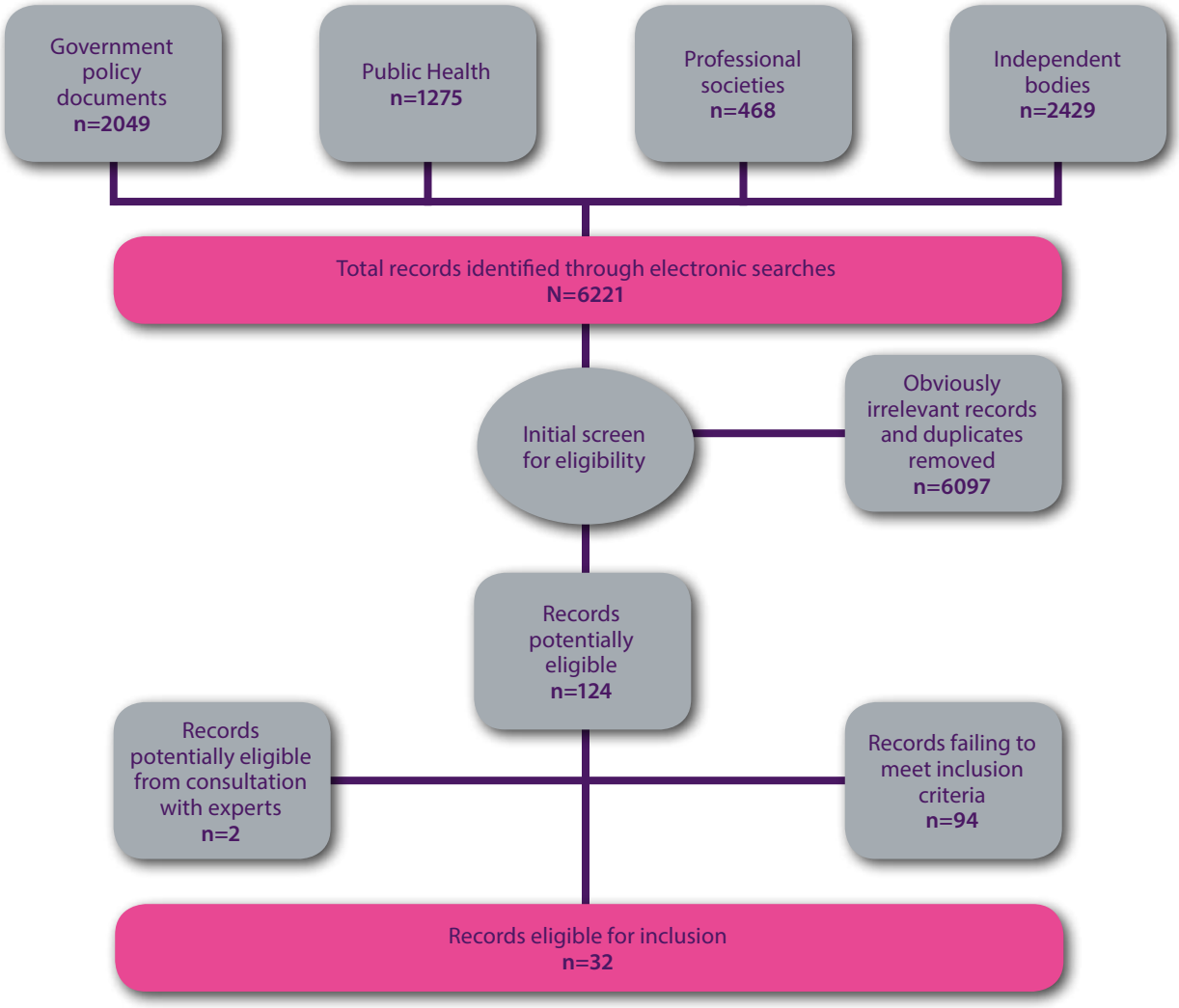
Search results

A total of 6221 records were identified that contained at least one of the search terms used following searches conducted of a total of 28 data sources. Of these, 124 records were selected for further detailed screening in order to identify if they fulfilled selection criteria to inform this review. This led to the removal of 94 records that were initially screened and thought to be relevant but on further assessment did not meet the inclusion criteria. Reasons for exclusion included clearly not relevant to the objective (e.g. news piece, information resource or related to person centred healthcare) on the basis of record date or that the scope of 'personalised' within the record was largely around treatment of existing disease or therapeutics.

A final list of 32 records was eligible for inclusion in this review and they were categorised according to the different stakeholder groups mentioned above. The majority of the records could be attributed to independent bodies (n = 15), and similar numbers of records were classified as government (n = 8) or public health (n= 6). A small number were attributed to the professional category (n=3). This is perhaps unsurprising given the nature of policy development, with independent organisations having more of a capacity and interest in identifying and assessing scientific developments that are likely to impact on healthcare. Below we give a summary of the findings under each category.

Figure 3 provides a summary of the review process and numbers of articles identified.

Figure 3 A schematic of the review process used to identify UK publications



Government

Of the eight documents attributed to government, four were published by the Scottish government [146, 147, 148, 149], one by the Welsh government [150] and three by the Department of Health [151, 152, 153].

Although these documents discuss personalised healthcare, they do not mention personalised prevention in detail and only three documents alluded to personalised prevention. The Welsh government consultation document - *Genomics for personalised medicine* - outlines the key initial actions as part of a 5-10 year plan, to develop medical and public health genomics services in Wales. It acknowledges personalised prevention as one of the 'five Ps' of precision medicine.

The Scottish government cancer strategy document [148] and a document published by the Department of Health providing advice to local authority and NHS commissioners about actions to improve cardiovascular disease outcomes [152] both refer to using appropriate risk stratification.

The Scottish government cancer strategy is the only document that alludes to personalised prevention in the context of breast cancer. This is in the context of the Act Well programme – a personalised breast cancer risk reduction programme offered to women attending routine breast screening clinics. One of the actions set out by the document is to examine if such a programme is effective and should be rolled out.

Public Health

Five of the documents attributed to public health were authored by NHS England [154, 155, 156, 157, 158] and one was the report of the Chief Medical Officer in 2016 [159]. All of these documents referred to personalised healthcare in the context of improving provision of therapeutics based on molecular diagnostics and targeted treatment.

Prevention is recognised as an important goal in the NHS Business Plan [155] as is personalised medicine; however, mechanisms to achieve this based on stratification are not discussed. This is also the case for the NHS Five Year Forward View[158].

The NHS England Personalised Medicine Strategy and linked document *Improving outcomes through personalised medicine* set out a vision for personalised medicine in the NHS [154, 157]. Although these documents do not discuss personalised prevention in the context of breast cancer, it is mentioned in a wider context: 'genomic technologies and other diagnostics will be able to identify people most at risk of disease even before the onset of their symptoms. Earlier detection will open up the prospect of new treatment options and support people to make informed lifestyle choices.'

Much of the discourse in relation to personalised prevention was in the cancer sphere; however, apart from the Cancer Strategy for England, this discourse has mainly been in relation to treatment rather than prevention. The Independent Cancer Task Force developed a five-year action plan for cancer services and published its strategy in 2015. Amongst its 96 recommendations was that NHS England and PHE should work to evaluate the potential for risk-based prevention and surveillance programmes based on germline genetic profiling.

The Government has accepted this recommendation and implementation is being led by NHS England's National Cancer Transformation Board, with an Independent National Cancer Advisory Group established to advise and assess progress. This was followed by publication of an implementation plan by NHS England in May 2016 and a report in October 2016 providing an update on progress made in delivering the recommendations of the Cancer Strategy. Although these documents discuss stratified pathways of care, it is in the context of treatment rather than prevention.

The Chief Medical Officer's annual report is the only document with an extensive discussion on personalised prevention, with a chapter dedicated to this topic and risk-stratified cancer screening, with discussion of stratified breast cancer screening.

Independent

Of the fifteen independent reports identified the majority were published by the PHG Foundation (n=7) [160, 161, 162, 163, 164, 165, 166]. Other reports focusing on personalised medicine were published by the Nuffield Council of Bioethics (n=2) [167, 168] and Academy of Medical Sciences (n=1) [169]. The Nuffield Council of Bioethics is an independent charitable body that examines and reports on bioethical issues related to biomedical research. The Academy of Medical Sciences has a mission to 'advance biomedical and health research and its translation into benefits for society'. Four were documents responding to the cancer strategy in England by Cancer Research UK and The All Party Parliamentary Group (APPG) on Cancer [170, 171, 172, 173]. Also included is *the Accelerated Access Review (AAR)*[174] an independently chaired report commissioned by the government to examine how to improve access to innovative medicines and technologies.

Apart from publications by the PHG Foundation, none of these documents contain extensive discourse in relation to personalised prevention or personalised prevention for breast cancer.

Professional

The search was only able to identify three documents attributable to the clinical category and all three were authored by the Royal College of Radiologists and/or the Faculty of Clinical Oncology [175, 176, 177]. Although all of these documents discussed personalised healthcare, it was generally in the context of treatment as opposed to prevention. The submission by the Royal College of Radiologists (RCR) to the Cancer Taskforce provides the viewpoint of the RCR on ten topics, of which one is prevention and screening. They acknowledge the importance of preventative measures in relation to shared risk factors (tobacco, alcohol and weight management), but also call for progressive adoption of biomarkers for stratifying patients and monitoring treatments. They also highlight the workforce capacity issue in imaging which can have an impact on providing more personalised prevention. This is in light of the fact that increased personalisation may require more imaging information at an initial stage to stratify individuals.

Conclusions

As a whole in the United Kingdom there is extensive discourse around personalised healthcare but little around personalised prevention. Personalised prevention when discussed is most often described in the context of risk stratification based on genetics. Personalised breast cancer prevention was only mentioned once.

The most extensive discussion surrounding personalised prevention could be found in documents from the PHG Foundation who have conducted extensive analysis of the subject. In summary, personalised prevention is believed to be a complementary approach to classical public health, population based approaches. Personalised prevention, largely based on genomics is already being used in the fields of rare diseases and cancer. Its current impact on common complex disorders is through enabling the identification of sub-sets of individuals across a number of disease areas who are at high risk due to genetic factors, thereby enabling their differential treatment. However, there are currently few systematic approaches being implemented to identify these individuals.

Recommendations have been made by PHG Foundation to achieve more widespread uptake of personalised prevention. This includes calling on policy makers to consider of how health systems can harness technological advances to collect and utilise individual data, work together with individual citizens to enable them to take greater responsibility for their health and identify mechanisms to deliver preventative medicine.

5.5 Personalised prevention – Australia

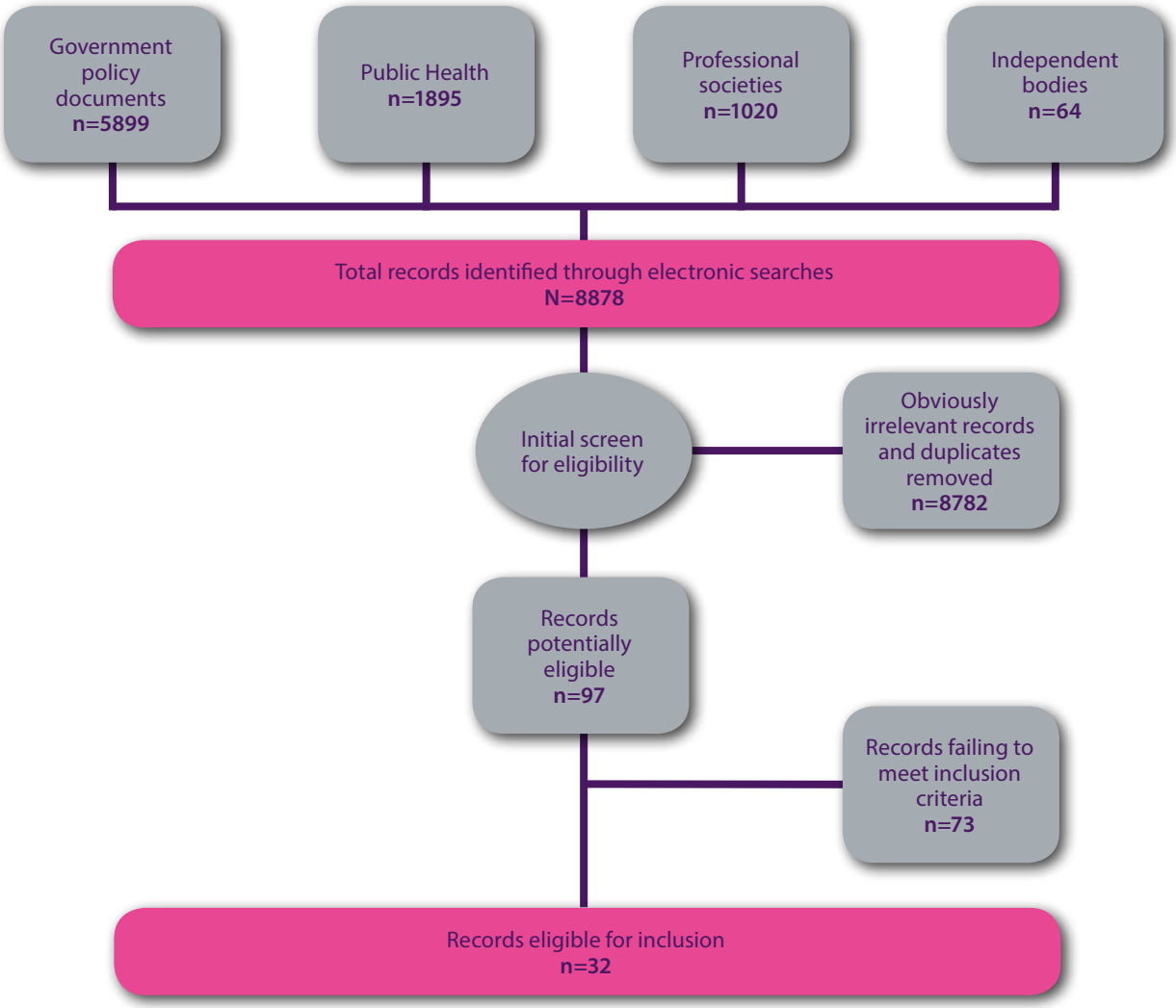
Search results

Following searches conducted of 26 data sources a total of 8878 records were identified that contained at least one of the search terms used following searches conducted of a total of 26 data sources. Of these, 97/ records were selected for further detailed screening in order to identify if they fulfil selection criteria to inform this review. This led to the removal of 73 records that were initially screened and thought to be relevant but on further assessment did not meet the inclusion criteria. Reasons for exclusion included clearly not relevant to the objective (e.g. news piece, information resource or related to person centred health care), on the basis of record date, scope of 'personalised' within the record was largely around treatment of existing disease or therapeutics.

A final list of 24 records were eligible for inclusion in this review and they were categorised according to the different stakeholder groups mentioned above. The majority of the records could be attributed to government bodies (n = 12), similar numbers of records were classified as professional (n = 6) or independent (n= 6). We did not classify any under public health, however, this is due to the fact that many public health documents were published by state or the federal governments and hence are encompassed within this category.

Below we give a summary of the findings under each category and Figure 4 provides a summary of the searches.

Figure 4 A schematic of the review process used to identify Australian publications



Government

Of the twelve documents attributed to government, two were federal government publications [178, 179], and the remainder state government publications. Personalised prevention is mentioned in all these documents, mainly as an important area of development. It is discussed more extensively in the context of genetics in documents such as the *Genomics Healthcare for Victoria* – a discussion paper [180] produced as part of the process of developing a new genomics services strategy for Victoria, the *Victoria Cancer Plan 2016* [181] and the *Queensland Biomedical and Life Sciences 10-year Roadmap*. However, the emphasis in many of these documents is on precision therapies rather than personalised prevention. Personalised prevention is also mentioned in the context of the Digital Health Strategy for Queensland [182].

We were unable to identify documents with a fuller discussion on personalised prevention or personalised prevention of breast cancer.

Professional

All the publications (n=6) identified under this category were articles published in *Australian Family Physician* a peer-reviewed journal published by the Royal Australian College of General Practitioners. There is a discussion within these articles of the impact of advances in genetics and other point-of-care testing on the practice of medicine. Much of the discussion is surrounding issues of interpretation of increasing amounts of data, access and sharing of this data, ensuring primary care are aware of the evidence base surrounding innovations and the impact of the availability of innovations on ensuring equitable healthcare.

Independent

Five of the six documents attributed to independent organisations were published by the ATSE (Australian Academy of Technology and Engineering) – an independent, non-government, not-for-profit organisation made up of individuals from academia, government, industry and research. Developing technologies for personalised prevention is an area the ATSE identified as an important area with relation to health technology in its 2013-2017 and 2017-2020 strategy plans. Four of the identified documents were position statements that support this strategic plan and within these there is a recognition that a number of technologies such as wearables, data sharing and genomics can enable personalised prevention as they enable collection of individual specific information. Personalised prevention was also discussed in an article in ATSE Focus a magazine produced to stimulate discussion and public policy initiatives on key topics of interest to the Academy and the nation. Many articles are contributed by ATSE Fellows with expertise in these areas. The article by Carrie Hilliard discusses the impact of technology on the prevention agenda, and recognised genetics as the common denominator to deliver more personalised healthcare [183].

The other independent publication identified was a report commissioned by the Government of New South Wales aimed at gathering evidence on the changing landscape of the genetic counselling workforce. Although there is no extensive discussion on personalised prevention, the document highlights that several GPs felt that, as a result of increasing awareness of breast cancer and *BRCA1*, they are seeing increased demand for genetic testing and that adequate resources are needed at the primary care level to counsel people.

Conclusions

Within different policy documents there is an emphasis on personalised and preventative healthcare as an important policy goal. However, apart from the recognition that a number of emerging technologies can contribute to achieving more personalised and preventative healthcare, there is little discussion on how to achieve this outside the context of clinical genetics. We were unable to identify any discussion of personalised prevention of breast cancer within the documents we identified in this exercise.

5.6 Summary of policy discourse in relation to personalised prevention

Though personalised prevention as a concept has gained traction in many government policy documents as evidenced by the commitment to develop methods to enable it, there is little discussion on specific mechanisms to deliver this or a vision in this area especially in relation to breast cancer. Furthermore, as evidenced in many policy documents, as personalised prevention aims to place individual citizens at the centre of care, this is often conflated with person-centred care. The latter aims to ensure that individual needs are met and consulted in providing their care. To some extent technologies that enable personalised prevention, especially those that are more patient facing (e.g. Apps) also enable patient centred care. However a distinction is that personalised prevention is based on biological stratification of individuals in addition to considering their individual wishes and values.

Much of the dialogue around personalised prevention is centred around the contribution of genomics. This probably reflects the fact that current capabilities in endogenous biological stratification are largely only possible on the basis genetic factors. However, in those who do not have a significant family history or a specific mutation has not been identified, a greater understanding is needed of the contribution of genetic versus non-genetic factors. Personalised prevention in relation to breast cancer was only discussed in the context of stratified prevention.

Personalising screening through genetics was examined in the European Commission funded COGS (Collaborative Oncological Gene-Environment Study) project. This project as well as a number of other research initiatives indicate that including genetic data along with age could improve the accuracy of risk prediction and allow more targeted screening. A number of studies are underway in different countries to examine this approach including the PROCAS study in the UK and the WISDOM study in the United States.

Conclusions

A considerable amount is known about risk factors associated with breast cancer. However, the mechanism and relative contribution of different risk factors to the development of disease in individuals is still not fully understood. An understanding of the impact of various risk factors at the individual or sub-population level is important in order to enable more personalised prevention at the population level.

Obtaining precise information on risk factors and their impact at an individual/sub-population level remains a challenge. This stems from difficulties in measuring exposures consistently in studies and the fact that the outcomes that are examined (incidence or mortality) occur late in the disease pathway. Challenges are also created by the interrelationship between risk factors and their interaction; for example in investigating post-menopausal breast cancer.

Consideration also needs to be given to factors such as the use of HRT, numbers of reproductive cycles and age at which children were born. The variable impact of these risk factors on particular molecular subtypes of disease and in particular populations (e.g. high risk individuals due to genetic susceptibility) is currently not fully understood.

Examination of the global and national policy landscape indicates that there is recognition that breast cancer is an important cause of mortality and morbidity [54] and improving primary prevention is a goal of many policy makers. The main approach to prevention is through health promotion to inform and empower individuals to reduce their own risk. However, these messages are not targeted at specific at-risk groups or modulated to provide differential information to different at-risk groups. Established screening programmes enable early detection and treatment at a population-wide scale. Although preventative strategies are available for those at high/moderate risk as a result of genetic factors or family history, identification of these women is opportunistic. In most countries pathways of care are most well established for those who are considered high risk due to possessing *BRCA1/2* mutations.

Recent advances in science and technology are contributing to our ability to characterise individuals as well as develop novel therapies. Detailed characterisation of individuals requires tools to accurately measure endogenous biomarkers (e.g. genes, proteins and metabolites), phenotypes (e.g. height, weight, breast density) as well as external exposures (e.g. diet, level of physical activity etc.). Developments in genetic, imaging and wearable technologies are enabling much more accurate characterisation of individual behaviours and exposures. This, coupled with advances in mechanistic and machine learning models, can enable efficient analysis and modelling of this data for more accurate prediction of future development of disease.

There is a desire to harness this shifting technological landscape to drive more sustainable healthcare by improving personalised prevention. As such, personalised healthcare and personalised prevention are gaining prominence in policy debates. However, there is still more emphasis on therapeutics as opposed to prevention. Although examples are given, particularly from the viewpoint of genomic technologies and their role in prevention, these are limited to the identification of those at high risk as a result of family history.

We could not identify extensive discussion surrounding personalised breast cancer prevention. References that were made to personalised breast cancer prevention were around the consideration of stratified screening pathways.

Our investigation suggests a lack of discourse at policy level around personalised prevention for breast cancer. However, we designed our search strategy to be sensitive rather than specific, and given the breadth of the field, it is likely not all discussion has been captured. That said, by consulting with experts we have endeavoured to ensure that key documents were not missed and are confident this study provides an illustration of the current discourse in the United Kingdom and Australia. Discussions with experts from other countries suggest a similar picture globally.

6. Appendix: Grey literature search protocol

7.1 Objective

Investigate the inclusion of personalised breast cancer prevention within the discourse of public health and policy makers through examining how personalised prevention is viewed by different stakeholders and what are the key impact areas. We define personalised prevention as the combination of better differentiation between individuals based on biological characteristics and the offer of tailored interventions. Thereby allowing a move away from a 'one size fits all' approach to one that seeks to determine individual risk and provide appropriate interventions on the basis of this risk.

Key stakeholders: Government, public health, clinicians and key independent bodies.

7.2 Methods

Search strategy

A grey literature search strategy was developed to identify policy documents, blogs or commentaries relating to personalised prevention. It was anticipated that the literature in this area would be limited and included within the wider context of personalised healthcare; therefore the search strategy was intended to be sensitive rather than specific. Data sources to be searched were identified through consultation with experts to ensure they covered the relevant stakeholder groups. The data sources are listed in table 6. The search strategy used the following search terms:

- Personalised healthcare
- Personalised medicine
- Personalised prevention
- P4 medicine
- Precision medicine
- Stratified medicine
- Individualised medicine
- Study inclusion criteria selection

Only records meeting the following criteria will be included in this review:

- Published between 2012-2017
- Is a policy document, blog, commentary
- Provides a stakeholder perspective
- The discussions around personalised prevention are within the boundaries of our description

Study exclusion criteria

- Published prior to 2012
- Related to therapeutics/treatment of existing disease
- Related to person-centred care

Data extraction

All records identified as eligible following the initial screen were stored in an Endnote database with duplicate records identified and removed. A single reviewer reviewed titles and scanned records to identify potentially relevant records for inclusion. The final list was validated by cross checking with experts to ensure eligibility.

Data extraction was carried out by a single reviewer using a standardised data extraction form and cross checked by a second reviewer. Extracted data included the following:

- Document source
- Year published
- Author
- Record type (i.e. blog, policy report etc.)
- Summary of purpose of document
- Summary of purpose of document
- Which "personalised" term is mentioned
- Context in which term is mentioned
- Is personalised prevention mentioned
- Context of discussion on personalised prevention
- Is breast cancer mentioned in the context of personalisation
- Other conditions described with regards to personalisation

- What areas of practice are they described in relation to?
- Any barriers to implementations specified?
- Opportunities for implementation specified?

Data analysis

A narrative synthesis was undertaken to describe the volume and types of information and the results of the analysis of relevant documents. Similarities and differences in findings for the three countries will be discussed.

Table 6 Data sources used in grey literature research

Stakeholder	Data Source	UK	Australia
Government	National government policy documents	Gov.uk Scottish government website Welsh government website Northern Irish government website	Australian Federal Government State governments: New South Wales Northern Territory Queensland South Australia Tasmania Victoria Western Australia Office of population health genomics
Public Health	Key organisations involved in public health	NHS England NHS Scotland NHS Wales NHS Ireland Public Health England UK National screening committee	Department of health Cancer Australia COAG Health Council Australian Institute of Health and Welfare Public Health Association Australia Australian Health Promotion Association Australian Health Care Reform Alliance
Professionals	Clinical societies	Royal College of General Practitioners Royal College of Surgeons Association of Cancer Physicians Royal College of Radiologists Royal college of Physicians British Society for Genetic Medicine The Association of Clinical Genetic Science	Royal Australasian College of GPs Clinical Oncology Society of Australia Royal Australasian college of surgeons Royal Australasian college of Physicians The Royal Australian and New Zealand college of Radiologists Human Genetics Society of Australasia
Independent bodies		Academy of Medical Sciences Royal Society Cancer research UK Cancer research fund Nuffield Trust Nuffield Council on Bioethics Kings Fund Macmillan Breast cancer now PHG Foundation	National health and medical research council Cancer council Victoria ATSE

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