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REVIEW

Breast cancer epidemic in the early twenty-first century: evaluation of risk factors, cumulative questionnaires and recommendations for preventive measures

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Abstract Rapidly increasing incidence of breast cancer is a new social challenge resulting from a spectrum of internal and external risk factors which appear to be well accepted as an attribute of the early twenty-first century, being, however, new for female sub-populations compared to the past. These include altered socio-economical conditions such as occupational exposure, rotating shift work, specific environmental factors (increased pollution and environmental toxicity, altered dietary habits, quality and composition of meal) as well as consequently shifted and/or adapted physiologic factors such as lower age at menarche, late age of first full-term pregnancy, if any, shorter periods of breastfeeding and later menopause. Consolidated expert statements suggest that over 50 % of all breast cancer cases may be potentially prevented by risk reduction strategy such as regulation of modifiable risk factors. Currently available risk assessment models may estimate potential breast cancer predisposition, in general; however, they are not able to predict the disease manifestation individually. Further, current deficits in risk assessment and effective breast cancer prevention have been recently investigated and summarised as follows: gaps in risk estimation, preventive therapy, lifestyle prevention, understanding of the biology of breast cancer risk and implementation of known preventive measures. This paper overviews the most relevant risk factors, provides recommendations for improved risk assessment and proposes an extended questionnaire for effective preventive measures.

Keywords Breast cancer · Epidemic · Predictive preventive personalised medicine · Individualised patient profile · Questionnaire

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Introduction

Currently recognised breast cancer (BC) spread reaching an epidemic scale (about half of million deaths are caused by BC annually [1]) is a major public health problem which negatively impacts the life quality of several millions of patients and their families worldwide, economical burden, healthcare systems and society as a whole. Globally, the highest BC incidence appears in high-income regions: North America, Northern and Western Europe, Australia and New Zealand [2]. Traditionally, lower incidence in Asiatic regions is changing dramatically into permanently increasing BC rates for both younger and older women [3–5]. Rapidly increasing incidence of BC is a new social challenge resulting from a spectrum of internal and external risk factors which appear to be well accepted as an attribute of the early twenty-first century, being, however, new for female sub-populations compared to the past. These include altered socio-economical conditions

such as occupational exposure, rotating shift work, specific environmental factors (increased pollution and environmental toxicity, altered dietary habits, quality and composition of meal) as well as consequently shifted and/or adapted physiologic factors such as lower age at menarche, late age of first full-term pregnancy, if any, shorter periods of breastfeeding and later menopause.

This paper is motivated by the accumulated evidence and more and more consolidated expert statements that over 50 % of all breast cancer cases may be potentially prevented by regulation of modifiable risk factors such as lifestyle and weight control, regular physical activity and minimisation of alcohol consumption. Currently available risk assessment models such as Gail and Tyrer-Cuzick may estimate potential breast cancer predisposition, in general; however, they are not able to predict the disease manifestation individually. Further, current deficits in risk assessment and effective breast cancer prevention have been recently investigated and summarised as follows: gaps in risk estimation, preventive therapy, lifestyle prevention, understanding of the biology of breast cancer risk and implementation of known preventive measures [6].

This paper overviews the most relevant risk factors, provides recommendations for improved risk assessment and proposes an extended questionnaire for effective preventive measures.

Paper design

Breast cancer is well recognised as a multifactorial disease [1]. Further, it has been well justified that breast cancer research and practical management both demand an optimised approach based on multilevel diagnostics [7]. In order to be able to create this kind of approach in the closest future, the broad spectrum of factors and corresponding levels of diagnostics should be better understood. Keeping in mind this major goal, our review article analyses the currently available knowledge and corresponding literature sources considering the most frequent disease contributors, namely specific socio-economic conditions, physiological factors, environmental contributors, metabolic alterations, as well as (most likely) relevant syndromes and disorders.

Since familial breast cancer causes about 5 till 10 % of the overall disease cases being strongly dependent on the genetic component versus 90 % and more of the sporadic breast cancer cases which other factors may play a decisive role for, the genetic component was not in the focus of our current paper dedicated mainly to the sporadic cases as the absolute majority of the breast cancer patient's cohort.

Modelling of the risk assessment to be further performed in order to improve the currently available *Gail*, *Tyrer-Cuzick* and other approaches is considered as the ultimate follow-up step based on the summarised knowledge (incl. current article), individualised patient profiles and computerised breast cancer risk assessment (accurate statistical analysis, big data management, machine learning process and eHealth application), in order to improve predictive and preventive medical approaches in the overall breast cancer management [8].

Physiological risk factors and recommended preventive measures

The time period between menarche and first full-term pregnancy is the most susceptible for breast carcinogenesis

The time frame between the first menstrual period and the first full-term pregnancy is the most susceptible for breast cancer carcinogenesis [9]. Lower age at menarche (early puberty, e.g. due to increased protein and fat percentage in the dietary composition) and late age at the first full-term pregnancy (altered occupational exposure such as professional career) are attributable to females in the early twenty-first century compared to the past. This leads to highly increased hormonal stress resulting in an increased number of pre-lesion sites in breast tissue, longer time period between these two events, higher hormonal stress and, consequently, more pronounced predisposition to breast cancer development later in life. In this specific condition, lifestyle plays a crucial role in either preventing or, in contrast, facilitating the formation of premalignant lesions in functional breast tissue, depending on a balance between protective and destructive factors such as alcohol intake [10], inappropriate dietary habits, low quality of meal and sleep deficits.

Late first full-term pregnancy is a dominant risk factor for breast malignancies

Increased and altered professional occupation of women (see also the sub-section "Internal and external stress factors") that seems to be a typical socio-economical component of the early twenty-first century is recognised as one of the risk factors for breast cancer development. Successful career development and extremely high professional competition requires pro longed periods (due to one, two or even three high school diplomas) of educational process. A direct consequence of that is a late first full-term pregnancy (over the age 30–40 years) that is getting standard in female sub-populations and increasing dramatically breast cancer incidence [6]. Taking into consideration the above-stated paragraph that the period between menarche and first full-term pregnancy is the most susceptible one for breast carcinogenesis, the risk by a late first full-term pregnancy is getting more understandable, due to the sufficiently prolonged period of the extensive accumulation of pre-cancerous lesions.

Cumulative risks by early menarche, late menopause and low number of children

Altered dietary habits and socio-economical and environmental conditions that are usual for the early twenty-first century altogether lead to synergistic effects resulting in early menarche (below 10 years), late menopause (over 50 years) and low number of children born. Consequently, the total number of menstrual cycles and ovulations which an averaged woman does experience over her lifespan now is several times higher compared to that in the past. This dramatically increases the exposure to the hormonal stress, which breast tissues are particularly sensitive to extensively accumulating pre-cancerous lesions over the extremely prolonged time of the hormonal stress exposure. This knowledge led to the consideration of a protective therapeutic approach by oestrogen receptor blockers such as tamoxifen, raloxifene and fulvestrant [11, 12].

Long periods of breastfeeding have protective effects against breast malignancies

A negative correlation between the overall duration of breastfeeding and breast cancer incidence has been demonstrated. Therefore, a prolonged (over 12 months) breast feeding should be encouraged for many reasons including evidence-based reduction of breast cancer risks and positive health impacts for both mother and child [13].

Inverse association between physical activity, energy restriction and breast cancer risk

Nowadays, sedentary lifestyle is getting more and more ubiquitous that has adverse health effects in general and specifically increases breast cancer risk [14]. There are several attributes of physical inactivity with pronounced synergistic effects of cumulative breast cancer risk factors such as ageing-related processes, overweight/obesity, altered insulin sensitivity, inflammation and increased cytokine and oestrogen production. In contrast, energy restriction is a well-known longevity contributor; further, regular physical activity reduces exposure to sex hormones [15], improves insulin sensitivity, immune and antioxidant defence capacity, and activates tumour suppressor genes [14, 16]. Further, weight control is a powerful instrument to reduce breast cancer risk as discussed below.

Family history

General predisposition to cancer

General predisposition to cancer consists of two major components: on the one side, a genetic (inherited) component, and on the other side, a cumulative effect of non-genetic risk factors (environmental, lifestyle, dietary habits, etc.). Consequently, the family history provides important information which may indicate inborn predisposition to cancer to be carefully considered for early screening, risk reduction strategies and most effective treatments. Cancer (any type) history in the family may increase breast cancer risk for the next generations [17]. Further, carriers of germline mutations in BRCA1/2 are predisposed to both breast and ovarian cancer types [18]: in case of these patient cohorts, an urgent need in predictive diagnostics is well justified for more effective preventive measures and targeted treatments. In the USA, promising results have been recently demonstrated by the study performed within the population of privately insured women who are members of an integrated healthcare system and whose information on ovarian cancer risk as well as personal and family histories of cancer is available. The conclusion was that well-organised systematic population screening might effectively lower the morbidity and mortality for breast, cervical and colorectal cancers in the same population screened [19]. In summary, there is a clear consensus reached amongst the experts in the field: predictive approaches of laboratory diagnostics should be applied to estimate individual risks through genetics clinic within the healthcare system. Currently, identification of predisposing genes is not provided to the population as a whole but only through familial breast cancer cases that comprise 5 till 10 % of all breast cancer cases.

Familial breast cancer (BC)

Only a small portion of the overall patient pool demonstrates BC history in the family, namely 5 to 10 % of BC diseased in more than one generation. The cause of hereditary BC is the genetic component with the most common inherited mutations reported for BRCA1 and/or BRCA2 genes. Although in some BC-predisposed families with BRCA1/2 mutations the lifetime risk may reach 80 % and more, the average risks range between 45 and 65 %. This statistical data emphasise that the genetic component alone is not decisive enough for BC development: the crucial one is the individually managed interplay between genetic and non-genetic risk factors (environmental, lifestyle, dietary habits, etc.).

Internal and external stress factors

Environmental factors

There is an accumulating evidence that about 90 % of cancers may be linked to environmental exposures [20, 21]. Environment and lifestyle and behaviour bridge together internal and external stress factors, and the best investigated examples of which are listed below:

- Industrial air pollution [22]
- Toxic environmental contamination (heavy metals and genotoxic agents, etc.) [23]
- Drinking water and food contamination [24]
- Ionising radiation exposure (professional exposure, medical examinations, etc.) [25, 26]
- Tobacco smoke (both active and passive) [27]
- Psychosocial stress factors (stressful interpersonal experience) [28]
- Nutritional risk factors (excessive alcohol consumption, etc.) [29, 30]
- Viral infections (e.g. by mutagenic effects) [31]
- Artificial/surgical implants (plastic surgery, dentistry, etc.) [32–35]
- Professional occupation in specific branches (production of toxic compounds, higher-status occupation, rotating shift and night work, flight attendants, etc.) [36–38].

The latter is subject to discuss in more detail; please see below.

Professional occupation in specific branches may strongly predispose to BC development: examples

Higher-status occupations are associated with elevated breast cancer risks A number of epidemiologic studies have demonstrated that socio-economical status is inversely associated with morbidity. However, paradoxical findings are reported regarding the elevated risk of breast cancer amongst professional women with higher-status occupation compared to housewives and women in lower-status occupations [39]. In particular, exercising job authority (e.g. by managerial occupation) defined as control over others' work was performed under stressful interpersonal experience and related to higher BC risks. The contextual stress was linked to prejudice, tokenism, discrimination, social isolation and resistance from subordinates, colleagues and superiors. In this condition, two synergistic mechanisms have been proposed as relevant for BC risk: pronounced psychosocial stress and pathophysiologic alterations in the oestrogen-related processes. The latter considers cumulative lifetime exposure to oestrogen (later age at first full-term pregnancy, lower parity and hormone replacement therapy), but this is also, due to inadequate health behaviour such as alcohol intake and sedentary lifestyle.

Rotating shift and night work: disruption of circadian rhythm and breast cancer risks Shift work (daily working hours other than the standard daylight period of time from 7–8 a.m. to 5–6 p.m.) is associated with risks for numerous health problems such as sleep disorder, fatigue, anxiety, depression, digestive and metabolic disorders, cardiovascular disease and cancer [40–42]. About 20 % of the European citizens who are involved in the night work conducted either in permanent or rotating regimes are considered to have the most disruptive effects on the circadian rhythm [43, 44]. Mechanisms which underlie BC risks include the suppression of melatonin and vitamin D synthesis, disruption of circadian rhythm, depression of immune system and sleep deprivation [42, 45–48]. Studies dedicated to the patient genotyping have collected evidence that a coding SNP in NPAS2 may modify the effects of shift work on breast cancer risk [36].

Flight attendants demonstrate elevated BC risk This professional group is at higher risk from BC that might be, due to occupation- and workplace-specific exposure which includes cosmic radiation, circadian rhythm and sleep disruption [37, 38]. Contextual factors such as the total number of hours of high-altitude and long-distance flights may play a role [49]. However, the most recent study emphasises the crucial role of the reproductive risk factors: later age at first birth and lower parity [38].

Syndromes and behavioural symptoms related to BC: fatigue, insomnia and Flammer syndrome

The most common behavioural sequelae of BC are fatigue, sleep disturbances, depression and cognitive impairment, some of which are essentially attributable to the reaction towards the diagnosis and treatment; other syndromes, however, are symptomatic for BC, in general, as a sub-optimal health condition which may predispose and/or additionally contribute to the cancer development. The most typical syndromes and behavioural symptoms related to BC are exemplified below.

Chronic fatigue as a sub-optimal health condition attributed to BC risk

There is growing evidence demonstrating the chronic fatigue as an attribute of cancer in general and specifically of BC, which appears for quite a long time before the clinical manifestation of cancer being particularly pronounced during and after the treatment with irradiation, chemotherapy and hormonal and biotargeted therapies [50–53]. Cancer-related fatigue ranges from 25 to 99 % in corresponding patient groups and has adverse effects on treatment outcomes; current in-depth research activities are dedicated to a better understanding of fatigue-specific molecular mechanisms and multifactorial risks such as genetic predisposition (family history), demographic, diverse biological, medical, psychosocial and behavioural factors [53]. Inflammatory processes may be involved in the aetiology of cancer-related fatigue prior, during and for a long time after the treatment completion [54]. Consequently, laboratory tests for monitoring of inflammatory biomarker panels (such as plasma concentration of

inflammatory cytokines) are of high relevance for cancer prediction, prevention and prognosis [55–57].

Immunity, latent viral reactivation as well as psychosocial and behavioural factors (stress factors, mood, sleep quality, physical deconditioning and healthy versus unhealthy BMI) play a role in combating fatigue. Consequently, effective prevention should be targeted to the person considering individual risk factors and proposing comprehensive prophylactic measures such as psychosocial intervention, physical exercises, regulation of BMI, normalisation of sleep and immunisation. A tight collaboration of innovative medical fields (such as hybrid technologies applied to predictive/early diagnostics and therapy monitoring) and traditional/complementary medicine (yoga, acupuncture, etc.) might represent the most optimal approach in a successful combat of the cancer-related fatigue.

Sleep disturbance in relation to cancer risk

As already described in the above paragraphs, rotating shift and night work is associated with breast cancer risk. The proposed synergistic mechanisms include circadian sleep disorder, melatonin suppression and inflammatory processes, the cumulative effects of which lead to BC development and progression. Well in consensus, several studies have demonstrated that the presence of insomnia/increased level of sleep disturbance alone has no direct impacts on breast cancer risks but is synergistic with other risk factors such as disruption of circadian rhythm, inflammation, hormonal and genetic predisposition, abnormal alcohol intake and unhealthy BMI [58–60]. On the other side, compared to the general population, the prevalence of insomnia is three- to fivefold higher in BC patients being associated with chronic fatigue, depression, pain and general disability to function [61–63]. This knowledge leads to a conclusion that only contextual risk factors with cumulative effects may have a real predictive power for BC development and outcomes and should be evaluated for each patient individually.

Flammer syndrome and potential formation of pre-metastatic niches in BC

Accumulating literature demonstrates that both initial tumours and secondary metastases need a "fertile" microenvironment effectively supporting their growth and progression [64]. The mechanisms "fertilising" the microenvironment for particularly effective cancer advancement are currently under extensive investigation [65]. Amongst pronounced risk factors, hypoxia is recognised as a strong driver of aggressive cancer types and active metastatic disease, e.g. triple-negative breast cancer. Systemic hypoxic effects have been demonstrated as forming pre-metastatic niches in distant organs [64, 66]. In this context, individuals with Flammer syndrome (FS) phenotype create a prominent cohort of individuals in sub-optimal health condition [67, 68]. FS individuals are of particular interest for a potential predisposition to aggressive BC phenotypes, due to the onset of symptoms early in life (puberty), more frequent in young women, hormonal risk factors (oestrogen-related migraine attack in reproductive years is frequent in FS), systemic hypoxic/ischaemic effects and involvement of systemic molecular events (altered stress response, multidrug resistance and energy metabolism; shifted regulation of transcription, apoptosis and adhesion; deficits in DNA repair efficacy; blood-brain barrier breakdown; extensive tissue remodelling accompanied by highly increased activity of the enzymatic core of metalloproteinases) into the pathogenesis of severe disorders in patients with FS phenotype [69, 70]. All these pathways are considered as evidently involved into effective cancer advancement [1]. FS phenotype as potentially predisposed to aggressive BC sub-types is currently under extensive investigation by our multicentred study [65].

Metabolic factors and disorders linked to BC risks

Abnormal BMI is linked to BC risks

Abnormal body weight may contribute to BC development and belongs to modifiable risk factors in the context of dietary intake and physical activity. In the term "abnormal body weight" in which both too low (underweight) and too high (overweight) BMI are incorporated, therefrom, overweight and obese subjects are considered and investigated more frequently as being at high risk for BC. The following are good reasons for that:

- Obesity is now a pandemic health concern with about half of billion of affected adults and one billion of overweight individuals worldwide [71]. Obesity increased dramatically in prevalence during last three decades presenting an independent risk factor for several types of cancer with comorbidities [31, 72];
- High medical costs associated with obesity demand approximately 9 % of all medical spending [73];
- Epidemiologic studies have well documented the association between obesity, increased fat tissue-driven oestrogen production and hormonal risks for oestrogen receptor-positive BC sub-type [74];
- Recent studies demonstrate that obesity is associated with worse breast cancer survival in pre- and post-menopausal women [75].

However, BC risk from overweight is different for age, pre- and post-menopausal women as well as BC sub-types. Hence, the reduced BC risk is associated with childhood obesity and higher BMI in early adulthood (age between 18 and 21) [6, 76–79]. Further, obesity was shown to be associated with an elevated risk for oestrogen/progesterone receptor-positive

postmenopausal BC but not for both oestrogen/progesterone receptor-negative pre- and post-menopausal women; this risk was further minimal for women who never took oestrogen-progestin therapy (see also the sub-section "Medication linked to the risk of BC" below) [80]. Further, for pre-menopausal women, an increased BMI (>25 kg/m^2) was associated with reduced BC risk.

Unfortunately, abnormally low BMI is considered and investigated less frequently as a risk factor for BC and poor outcomes: clear indication has been recently provided demonstrating that underweight women (BMI < 20) are at sufficiently higher risk for BC diagnosis and mortality compared to the standard range BMI = 20–25 [75].

The above-provided data led us to the conclusion that despite general trends, the association between the weight and breast cancer risk is highly individual and contextual (genetic predisposition, age, hormonal status, dietary habits, physical activity, amongst others). Ideally, the weight control should be accompanied by monitoring of complex patient profiles (family history, molecular profiles, medical imaging, etc.), in order to recommend healthy values optimised for the patient.

The role of metabolic syndrome and co-morbidities in BC development and progression

Diabetic history is demonstrated as a risk factor for BC development and worse outcomes compared to the general population; corresponding molecular mechanisms have been proposed [1, 31, 81]. Metabolic syndrome is characterised by increased levels of growth factors and inflammatory processes associated with BC development, progression and poor outcomes [82, 83]. BC-specific mortality has been reported to be highest for patients with a long history of diabetes (15 years and more), uncontrolled diabetes resulting in a higher risk of end-organ symptoms (e.g. heart and kidney failure) and cardiovascular disease with and without a diabetic history [83]. As for the latter, high impacts of cardiovascular co-morbidities in cancer development and progression recently led to creating a new sub-speciality *cardio-oncology* for more optimal management of long-term cardiovascular component [84].

Common risk factors, such as progressing age, abnormal weight, poor diet, physical inactivity and depression moderate the outcomes in the most frequent female (co-lateral) pathologies, namely type 2 Diabetes mellitus, cardio-vascular disease and breast cancer [85–87]. Moreover, modifiable risk factors persist from childhood and adolescence into adulthood and tend to cluster with synergistic adverse health effects for consequent manifestation of co-morbid pathologies [85, 88–96].

Currently, the cases in medical practice are not unique anymore, when a patient is taking around 20 and more medicaments prescribed for parallel treatments of single disorders, which are frequently considered as independent from each other. How much are they independent or overlap within the treatment frames? How much are single medications synergic with and contra-productive to each other? How much is multimodal medication depending on the profile of co-morbidities and on individual patient profile? All the questions should be obligatory addressed by long-term follow-up studies in accordance to reconsidered guidelines, in order to avoid treatments of single organs and pathologies instead of desirable synergic multimodal approaches [97].

Hyperhomocysteinaemia: multifactorial risks for cancer and cardiovascular and neurodegenerative diseases

The metabolic disorder of hyperhomocysteinaemia is associated with elevated risks for cancer and cardiovascular and neurodegenerative diseases [98–103].

Homocysteine (Hcy) is a non-essential amino acid generated metabolically by the *S*-adenosylmethionine-dependent transmethylation pathway. The function of Hcy is involved in the key regulatory pathways linked to DNA methylation, cellular oxidative-reductive response and proliferation—all the processes highly relevant for cancer development and progression [104].

Elevated levels of plasma Hcy have been shown to contribute to the pathophysiological metabolism of breast cancer [105]. However, this role of Hcy is contextual in connection to the altered folate metabolism, since higher BC risks have been confirmed in hyperhomocysteinaemia patients only, if linked to low folate status [106], and patients with altered genetic polymorphism in folate metabolism [107].

Depression is associated with worse clinical outcomes in BC patient cohort

A history of major depressive disorder places individuals at risk for poor mental and physical health, in particular, synergistically with other health adverse effects such as by sleep disturbance [108, 109]. These patients become more sensitised to subsequent stress situation resulting in a greater likelihood of worse clinical outcomes [110, 111].

There are evident cumulative effects between sleep disturbance, inflammation and depression risk in BC development and progression [112]. Hence, specific alterations have been reported in autonomic regulation and HPA axis activity amongst depressed women with metastatic breast cancer as well as elevation in pro-inflammatory cytokines in depressed BC patients [113, 114]. Further, depression is a synergic risk factor for cancer-related fatigue with a strong correlation between both depression and fatigue in the cancer population [115]. Although the exact causality between both constructs has not been properly investigated yet, fatigue appears as a symptom of depression [53]. Further, it might be of great interest to find out whether mood disturbance may predict

the onset and persistence of fatigue as attributes of cancer development and progression.

Alcohol consumption

Pathomechanisms of alcohol consumption in BC risks include oxidative stress and toxic effects by production of hormones and cancerogens [30]. In the BC context, alcohol intake is most critical in the time period between menarche and first full-term pregnancy, which is the most susceptible one for breast carcinogenesis as discussed above. Individuals who reported drinking alcohol almost daily at the age 16 to 23 years had more than fivefold elevated risks for benign breast disease (a BC risk factor as discussed below) compared to the "never/seldom drank" individuals [116]. Further, cumulative adverse effects have been reported between the alcohol intake and duration between menarche and first full-term pregnancy: each 10 g/day increase in alcohol intake resulted in BC risk elevated by 21 %, independent from alcohol intake after the first pregnancy; no risk increase has been reported for women with a shorter interval between menarche and first full-term pregnancy [10]. Stronger adverse effects of early life alcohol intake have been reported for females with a family history of BC and benign breast disease [117]. Further, alcohol intake is synergic with folate metabolism (see the above sub-section "Hyperhomocysteinaemia: multifactorial risks for cancer and cardiovascular and neurodegenerative diseases") [6]. Adult women who want to minimise BC risks should not drink not more than 1 unit of alcohol (1 unit = half a pint of 4 % strength beer or cider or 25 ml of 40 % strength spirits; a small 125-ml glass of 12 % strength wine as 1.5 units) daily and not more frequently than 5 days a week [6]. Moreover, moderate alcohol intake in adulthood after first pregnancy is linked to better life expectancy that should be balanced against recommending zero alcohol intake [118].

Migraine: higher or lower risk for BC?

Migraine is a heterogeneous disease with several sub-types described in the literature such as those with and without aura in both female and male populations. Hormonal fluctuations (such as menstruation cycle) certainly influence the occurrence of migraine attacks. Oestrogen production is an important player in the aetiology of both migraine and BC; therefore, an association between both diseases has been hypothesised in several studies with controversial conclusions: migraineurs are at reduced risk for BC [119–121] against increased risk for invasive triple-negative BC amongst migraineurs without aura [122]. Obviously, a more precise patient stratification (clear phenotypes such as Flammer syndrome with high frequency of migraineurs in the patient's cohort, hormone status, epidemiologic risk factor sets and complex patient profiles) might bring better clarity into the matter, in which sub-types of migraineurs might be at higher versus lower risk for BC.

Chronic inflammation as a contributor and prognostic factor in BC

Inflammatory processes are known to initiate and promote primary tumours and metastatic disease [20]. In turn, obesity, metabolic syndrome with co-morbidities, depression, hormonal stress, ageing as well as cancer therapy all are associated with systemic inflammation and BC risk as it has been already discussed above. Cytokines create the key protein cluster of inflammatory processes; their role has been demonstrated in breast cancer development, angiogenesis, metastatic disease and immunosuppression. Molecular panels of cytokines are attributable to the specific tumour stage, survival and malignancy progression [123].

Parameters and alterations of mammary glands linked to BC diagnosis

High-density breast tissue Mammary glands are directly or indirectly affected by the above-discussed factors, processes and pathologies that may trigger tumourigenesis in the breast tissue, parameter and alterations of which may be, further, BC supportive or protective. Hence, mammographic breast tissue density is crucial for increased breast cancer risk as well as false-negative and false-positive diagnoses [25]: BC risk for women with 70 % or more density is estimated as being 4.64-fold higher compared to women with less than 5 % density [124]. Examination utilising magnetic resonance imaging is the first choice to be met in the case of high-density breast.

Trauma and wound healing in BC predisposition Current hypotheses regarding the cancer initiation consider wounds and abnormal wound healing processes as strongly related to cancer risks [125]. Corresponding mechanisms propose cancer as a part of originally normal healing process which includes oncogene activation, cytokine secretion, stem cell recruitment and differentiation as well as extensive tissue remodelling. However, persisting wounds and decreased wound healing capacities may lead to the appearance of tumour cell mass in the traumatised tissue. Consequently, a history of breast trauma and investigation of molecular pathways involved in wound healing such as orchestrated metalloproteinases activity [1] may predict a potential predisposition of affected individuals to BC development and progression.

Benign breast disorder It is a clinically heterogeneous group of patients stratified according to proliferative versus non-proliferative lesions, with or without atypia. Non-proliferative lesions appear harmless, while proliferative benign breast disease increases a risk for BC development

Table 1 Proposed questionnaire

Parameter/status/ clinical condition in categories	Questions/ answers	Notes	Recommendations	References
Category 1: physiological factors				
Race/ethnicity		Traditionally, Asian females are at lower risk; however, individual BC risk depends on contributing risk factors such as stress and unhealthy lifestyle	Evaluation of individual patient profiles	[3–5]
Gender	Female/male	Females are more frequently predisposed to BC; however, familial BC is a risk factor for both females and males that impacts the next generations; obesity and diabetes are also risk factors for both females and males	Body mass index (BMI) and lifestyle control, regular re-evaluation of individual patient profiles to estimate contributing risk factors	[1, 6, 31, 41, 157]
Current age	In full years	BC risk is increasing with age	Corresponding preventive measures and regular monitoring of contributing risk factors are recommended	[6]
Menopausal status	Premenopausal/ postmenopausal	The absolute majority of BC cases are related to post-menopause; however, unhealthy lifestyle early in life increases the overall risks	Regular monitoring of contributing risk factors	[6]
Age at menarche (first menstrual period, FMP)	e.g. 13 years of age	Early (below 10 years old) age at FMP is a risk factor for BC; high impacts of correct lifestyle between FMP and age at the first full-term pregnancy	Shorting the time between FMP and age and the first full-term pregnancy; lifestyle control	[158]
Age at the first full-term pregnancy		Increased age (>30 years old) at the first full-term pregnancy is a risk factor for BC, in particular, at early FMP	Shorting the time between FMP and age and the first full-term pregnancy; lifestyle control	[159, 160]
Age at menopause (last menstrual period)	e.g. 49 years of age	Reproductive and menstrual exposures such as the age at menarche, age at first birth (AFB) and age at menopause have been consistently, but modestly, associated with breast cancer risk. The longest reproductive windows were 1.5–1.7 times more likely to have breast cancer compared with women with the shortest reproductive windows. Women in the highest quintile for the standardised AFB interval (≥15.3 years) are at a 52 % higher BC risk compared to women with the shortest intervals	Late menopause (over 50 years old) and a low number of born children are a strong BC risk. Regular monitoring of contributing risk factors and protective approaches by oestrogen receptor blockers are beneficial	[11, 12, 158]
Number of children born		The highest risk is observed for childless females		[6]
Breastfeeding in past	Per child in months	Breastfeeding decreases the risk	12 months or longer is recommended for breastfeeding per child	[13, 161]
Regular body activity	Times per week/month	Regular body activity is beneficial for BC prevention and better outcomes in breast cancer management	About 3–4-h walking per week may reduce breast cancer incidence, and women with early-stage breast cancer who increase or maintain their physical activity may have lower recurrence risk; 30-60 min of moderate to vigorous activity daily is recommended; in physically active subjects, the risk reduction is about 25–30 %	[14–16, 162–164]
Category 2: family history				
Number of first-degree relatives with breast cancer		Familial BC prevalence is 5–10 %; first-degree relatives with BC increase the risk for the next generations; however, synergic contribution by modifiable risk factors may be decisive	Early molecular diagnostics and systematic preventive measures are beneficial	[157, 165]

Table 1 (continued)

Parameter/status/ clinical condition in categories	Questions/ answers	Notes	Recommendations	References
Relatives with cancer	Yes, which kind of cancer/no	Relatives with cancer increase the risk for BC	Early molecular diagnostics and systematic preventive measures are beneficial	[17]
Category 3: internal and external stress factors				
Smoker	Yes/no	BC risk is increased the most (25 %) in women who started smoking younger than 18 years old, smoked longer than 35 years and, in average, smoked more than 25 cigarettes per day	Molecular diagnostics and systematic preventive measures are beneficial	[166–168]
Air pollution		Increased BC risks	Molecular diagnostics and systematic preventive measures are beneficial	
Water and/or dietary contamination		Increased BC risks	Molecular diagnostics and systematic preventive measures are beneficial	
Stressful environment	High/middle /low	Increased BC risks	Molecular diagnostics and systematic preventive measures are beneficial	[20, 21, 37–39, 49]
Rotating shift and/or night work	Yes/no	Increased BC risks	Molecular diagnostics and systematic preventive measures are beneficial	[36, 40–48, 169–172]
Category 4: syndromes and behavioural symptoms				
Chronic fatigue (ChF)	Yes/no	ChF may be an indicator for cancer development and prognostic factor for poor outcomes	Regular monitoring of contributing risk factors, molecular diagnostics and individual patient profiling	[50–57, 164, 173]
Sleep disorder	Known/unknown	Increased BC risk	Regular monitoring of contributing molecular pathways, molecular diagnostics and individual patient profiling	[58–63, 174–177]
Flammer syndrome (FS)	Yes/no (use of supplementary questionnaire for FS)	FS contributes to system hypoxic condition that may lead to adverse health effects in BC-predisposed individuals and metastatic disease in BC patients	Patient stratification; regular monitoring of contributing risk factors, molecular diagnostics and individual patient profiling	[64–68]
Category 5: metabolic factors and disorders				
BMI	Weight in kg/body length in m^2, e.g. 65 kg/$(1.65\ m)^2$ = 24	Childhood and adolescence: low BMI is a risk factor for BC later in life Adulthood: the most optimal BMI ranges from 20 to 25	Slightly increased BMI in childhood, adolescence and pre-menopausal women has a protective effect against BC; in contrast, a decreased weight is beneficial for post-menopausal women. The general recommendation is to keep a control over individually optimised weight; dietary habits and physical activity play a key role	[6, 74–77, 79, 80, 178, 179]
Diagnosed type 1/type 2 Diabetes mellitus (DM)	Yes/no (current glucose/ HbAc1)	Hyperinsulinaemia, rather than hyperglycaemia, is the major DM-related factor associated with an increased risk of BC	Prevention of DM and obesity; regular monitoring of contributing risk factors, molecular diagnostics and individual patient profiling	[1, 31, 81–83, 180–182]
Current level of plasma homocysteine/folate metabolism		Association of hyperhomocysteinaemia and hypomethioninaemia with BC, metastatic disease and development of drug resistance in BC cells	Regular monitoring of contributing risk factors (folate metabolism), molecular diagnostics and individual patient profiling	[98–107, 183]
Depression	Yes/no	Depression is a risk factor for BC outcomes	Regular monitoring of contributing risk factors, molecular diagnostics and individual patient profiling	[53, 108–115, 184–187]
Alcohol consumption	Regularity/ amounts	Increased alcohol intake is a risk factor for BC, particularly sensitive is the period between the first menstrual period and first full-term pregnancy	Alcohol intake should be avoided in early adulthood; later in life, it should not be more than 1 unit of alcohol (1 unit = half a pint of 4 % strength beer or cider or 25 ml of 40 % strength spirits; a small 125-ml glass of 12 % strength wine as 1.5 units) daily	[6, 30, 116–118, 132]

Table 1 (continued)

Parameter/status/clinical condition in categories	Questions/answers	Notes	Recommendations	References
			and not more frequently than 5 days a week	
Migraine	Yes/no	Migraine is considered as a selective risk factor amongst BC sub-types: more risky for triple-negative BC	Patient stratification; contributing risk factors (such as Flammer syndrome) should be evaluated; molecular diagnostics and individual patient profiling might be beneficial	[119–122]
Mastopathy and chronic inflammation (such as inflammatory bowel disease)	Known/unknown	Inflammation is one of the key mechanisms in BC development and progression	Evaluation of contributing risk factors, molecular diagnostics and individual patient profiling	[20, 123, 188]
Hysterectomy/breast trauma/other invasive approach on breast	Yes/no	Breast trauma is a BC risk factor	Evaluation of contributing risk factors and regular breast monitoring	[1, 125]
Benign tumours of breast	Known/unknown	Benign breast disease is a BC risk factor	Effective preventive measures (e.g. no alcohol intake early in life); evaluation of contributing risk factors and regular breast monitoring	[116, 126–133]
Atypical hyperplasia (AH)	Known, in years/unknown	AH is a strong risk factor for BC development	Evaluation of contributing risk factors and regular breast monitoring	[126]
Number of breast biopsies		Repeated breast trauma is a BC risk factor	Evaluation of contributing risk factors and regular breast monitoring	[1, 125]
Invasive breast cancer	Known, in years/unknown			
Ductal carcinoma in situ (DCIS)	Known, in years/unknown			
Lobular carcinoma in situ (LCIS)	Known, in years/unknown			
List of diagnosed pathologies		Co-lateral pathologies may provoke BC development and progression with poor prognosis	Molecular diagnostics and individual patient profiling	[84–96]
Category 6: medication				
Contraceptives	Yes, how long/no	Long-term use of contemporary oral contraceptives (OCs) and current use for ≥5 years are risks for BC	To be considered individually	[134, 159]
Menopausal hormone therapy	Yes, how long/no	Combined oestrogen-progestin menopausal therapy increases BC risk during the current use and a few years after	To be considered individually	[135–140, 189]
Any other current and past medication	No/yes, duration in years			
Category 7: medical examinations				
Frequency of regular mammographic examination		Mammographic examination demonstrates both benefits and harms	Frequency of mammographic examination should be recommended individually according to the patient profile evaluation	[25, 141, 142]
Frequency of any other regular breast examination/which one		Screening programmes resulted in the reduced mortality from BC	Diagnostic tools and frequency of BC examination should be recommended individually according to the patient profile evaluation	
Frequency of regular blood examination		Biomarker panels in the blood have been proposed to estimate and monitor BC risks	Regular blood tests are highly beneficial for molecular diagnostics and individual patient profiling/monitoring	[1, 144]

without and with atypia for 1.3–1.9 and 4.1–5.3 times, respectively [126–130]. Dietary factors are known to influence the risks of benign breast disorder, particularly early in life [131]. Alcohol intake early in life contributes to the risks of the disorder's appearance [116, 132]. Further, low BMI during childhood and adolescence increases the risk of benign breast alterations [133].

Medication linked to the risk of BC

Oral contraceptives or birth control pills may increase BC risk, if used over the long periods of time and actually for more than 5 years. Further, investigations in stratified patient groups revealed an increased breast cancer risk amongst women aged 20–44. The risk may be greater for patients with oestrogen-receptor negative and triple-negative breast cancer [134].

Menopausal hormone therapy

In order to help relieve symptoms of menopause, the so-called "hormone replacement", post-menopausal or menopausal hormone therapy (MHT) is used. However, there is clear evidence of associations between MHT and elevated risks for breast cancer [135]. Noteworthy, only the recent use of MHT seems to elevate BC risk that is, however, normalised within 2 years after the medication use is stopped [136]. BC risk varies, further, from type to type of the MHT being the highest for the combined oestrogen-progestogen therapy, in contrast to the oestrogen monotherapy [137]. Histological investigations demonstrated the prevalence of lobular and tubular BC associated with MHT risks rather than of the ductal one [138, 139]. Finally, polymorphisms in mitochondrial genes as well as in genes related to transmembrane signalling and immune cell activation have been demonstrated as a potentially modifying BC risk associated with the actual use of MHT [140].

Mammographic breast cancer screening: benefits and harms

Current breast cancer screening programmes utilise regular breast examination. Recent studies systematically investigate a balance between benefits and harms of them—the debate is sharply polarised now. The major benefit is an evident reduction in mortality from BC. However, mammography screening might result in adverse health effects, due to irradiation exposure and traumatic breast compression, false-negative and false-positive diagnoses and overdiagnosis [25, 141]. Further, the traumatic breast compression at carrying the mammographic examination is linked to discomfort and pain in the breast of screened women [142] and may contribute to cancer-driving alterations in the traumatised breast tissue as discussed above (see the sub-section "Trauma and wound healing in BC predisposition"). Incorrect diagnoses (false-negative, false-positive and overdiagnosis) result in both financial and psychological negative impacts and must be avoided [25]. In this term, main efforts are focused on a highly specific molecular biomarker panel which may allow distinguishing between latent cancer lesions and those which have a potential to progress into aggressive cancer and metastatic disease [65]. In this context, *regular blood examination*—as explained below—may be of great help as the optimal instrument for risk assessment [1].

Regular blood examination: complex patient profiling and disease-specific targets

With currently existing tools (medical imaging, etc.), there is currently no certain means of identifying lesions in breast tissue which are latent and will not progress into aggressive cancer disease [25]. On the other side, triple-negative BC tends to be a metastatic disease at very early stages of tumour initiation [143]. Consequently, novel predictive and preventive approaches are essential to be considered for BC management. At the molecular level, specific alterations associated with cancer predisposition and active carcinogenesis might be measured at the initiating stages. This action is in a good consensus with the new paradigm proposed to shift healthcare from reactive to predictive medicine. Therefore, promising measures in advanced breast cancer management should obligatorily include complex molecular patient profiling to detect alterations towards a pathology-specific signature; estimation of the individual breast cancer risk may be realistically performed, utilising the regular examination of the molecular profiles in blood samples. In the case of negative dynamicity indicating a development of adverse health effects, corrective treatment algorithms may be created according to the individual risk factors and affected molecular pathways [144]. Blood tests considering disease-specific targets demonstrated to be highly relevant for early BC detection such as at the level of miRNA [145], cell-free DNA [146–149], a protein cluster of metalloproteinases responsible for tissue remodelling [150–152], growth factors [153], SNP for angiogenesis genes [154], global regulatory factors [155], and others [1, 156].

Economical burden of breast cancer management is permanently increasing, negatively impacting the healthcare budgets. In contrast, regular patient check-up promotes an economically more attractive scenario for investment in healthcare. The costs related to the blood-based screening linked to the follow-up diagnostic measures need to be compared with the existing screening methods by mammography from viewpoints of health- and economy-related long-term outcomes. To give an example, a patient is diagnosed to have breast cancer at a progressive stage. In this case, the patient has to undergo surgery, chemotherapy, radiotherapy and endocrine treatment for several years causing the so-called "direct costs"

for the overall medical care. The indirect costs might be even higher, since this patient is not able to accomplish the work anymore or for a long period of time and/or not able to achieve a full-time equivalent becoming strongly handicapped in both professional and social activities as well as the family-relevant ones [144].

Conclusions and expert recommendations

There is a consensus amongst the experts in the field that over 50 % of all breast cancer cases are preventable. Although currently available risk assessment models may estimate potential breast cancer predisposition, they are not able to predict the disease manifestation individually. The creation of individual patient profiles and regulation of modifiable risk factors may be the most optimal predictive and preventive strategy. To our knowledge, the current paper provides the most complete overview of risk factors which contribute to and may have synergistic effects for the predisposition, development and progression of breast cancer and metastatic disease categorised as physiological factors, such as family history, internal and external stress factors, syndromes and behavioural symptoms, metabolic factors and disorders, medication and medical examination. The created questionnaire (see Table 1) is strongly recommended for its practical application by general practitioners, gynaecologists, endocrinologists, dieticians, paediatricians, medical geneticists and other field-relevant professional groups as well as by specialised medical centres focused on predictive, preventive and personalised medicine and women health. In this paper, a detailed description is provided for each factor of risk with corresponding mechanisms which may lead to the clinical manifestation of the disease. Correspondingly, the most effective measures are recommended.

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Authors' contributions Olga Golubnitschaja created the concept of the project, made the data interpretation and drafted the article. Manuel Debald contributed to the drafting of the paper. Kristina Yeghiazaryan and Martin Pešta contributed to the literature search. Walther Kuhn supervised the project at the Department of Obstetrics and Gynaecology. Vincenzo Costigliola contributed to the development of the project-relevant concepts. Godfrey Grech has overviewed the genetic aspects and corresponding strategies. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflicts interest None

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