Dear Vincent,

From your email I gathered that you required more information on the following aspects. I trust all of them have been covered in the sections below. I am not sure how much more detail you require (e.g. on possible mechanisms that could explain the possible pathways that isoflavones could be associated with), but have for now limited them.

Please note that the evidence have been compiled by myself and Inarie Jacobs (MSc Dietetics). She worked on the SABC study

1. About foods that apparently prevent or cause cancer….
2. One food that has raised a lot of interest is soybeans.
3. Could clarify whether soya contributes to breast cancer.
4. What about isoflavones?
5. Does the risk of breast cancer from soya differ based on ethnicity, say among African, Asian or Caucasian women?

Response to AfricaCheck request

By Christine Taljaard-Krugell and Inarie Jacobs

Contents

Dietary intake and Breast Cancer

Breast Cancer is globally the most common diagnosed cancer in women and the second leading cause of cancer mortality in various countries (WCRF & AICR, 2017; Castelló *et al*., 2017; Guerrero *et a*l., 2017). Dietary intake is one of the key modifiable risk factors contributing to BrCa risk. Hence, substantial research is being done on various aspects to obtain a better understanding to specific foods or patterns contributing to breast cancer risk. This overview aims to investigate the association between soy intake and breast cancer risk.

Risk reduction methods and factors regarding nutrition, diet, physical activity (PA) and body weight associated with cancer are regularly updated by the Continuous Update Project (CUP) (WCRF & AICR, 2018). The CUP report, reports on cancer survival and prevention led by World Cancer Research Fund International (WCRF) in partnership with the American Institution for Cancer Research (AICR) (WCRF & AICR, 2018). It is a strong, reliable scientific aid which supports up-to-date policies and guidelines for prevention and risk factors related to various cancer types (WCRF & AICR, 2018).

The CUP report, summarize the evidence on diet, nutrition and physical activity according to risk and according to different cancer types.

Findings on premenopausal breast cancer

There is strong evidence that:

- undertaking vigorous physical activity DECREASES the risk of premenopausal breast cancer
- being overweight or obese in young adulthood (between the ages of about 18 and 30 years) DECREASES the risk of premenopausal breast cancer
- being overweight or obese in adulthood before the menopause DECREASES the risk of premenopausal breast cancer
- breastfeeding DECREASES the risk of breast cancer (unspecified) in the mother
- consuming alcoholic drinks INCREASES the risk of premenopausal breast cancer
- being tall INCREASES the risk of premenopausal breast cancer
- greater birthweight INCREASES the risk of premenopausal breast cancer

There is some evidence that:

- consuming non-starchy vegetables might decrease the risk of oestrogen-receptor-negative (ER–) breast cancer (unspecified)
- consuming foods containing carotenoids might decrease the risk of breast cancer (unspecified)
- consuming dairy products might decrease the risk of premenopausal breast cancer
- diets high in calcium might decrease the risk of premenopausal breast cancer
- being physically active might decrease the risk of premenopausal breast cancer

Findings on postmenopausal breast cancer

There is strong evidence that:

- being physically active (including vigorous physical activity) DECREASES the risk of postmenopausal breast cancer
- breastfeeding DECREASES the risk of breast cancer (unspecified) in the mother
- being overweight or obese in young adulthood (between the ages of about 18 and 30 years) DECREASES the risk of postmenopausal breast cancer
- being overweight or obese throughout adulthood INCREASES the risk of postmenopausal breast cancer
- greater weight gain in adulthood INCREASES the risk of postmenopausal breast cancer
- being tall INCREASES the risk of postmenopausal breast cancer
- consuming alcoholic drinks INCREASES the risk of postmenopausal breast cancer

There is limited evidence that:

- consuming non-starchy vegetables might decrease the risk of oestrogen-receptor-negative (ER–) breast cancer (unspecified)
- consuming foods containing carotenoids might decrease the risk of breast cancer (unspecified)
- consuming diets high in calcium might decrease the risk of postmenopausal breast cancer

Evidence from the Continuous Update Report with regards to soy

The latest CUP report for breast cancer, **does not include** soy to be a protective or risk enhancing factor for the development of BrCa (WCRF/AICR, 2018).

Overall cancer prevention guidelines and guidelines for cancer survivors from the WCRF/AICR recommends individuals to eat a diet rich in wholegrains, vegetables, fruit and beans (WCRF & AICR, 2018). This specific guideline further states to include pulses like beans and lentils to be a part of one's daily diet. However, this guideline does not specifically emphasize the inclusion of soybeans or the amount of beans that should be consumed (WCRF/AICR, 2018).

Other guidelines include:

- Be a healthy weight
- Be physically active
- Limit consumption of fast foods and other processed foods high in fat, starches or sugars.
- Limit consumption of red and processed meat.
- Limit consumption of sugar sweetened drinks.
- Limit alcohol consumption.
- Do not use supplements for cancer prevention.
- For mothers: breastfeed your baby if you can.
- After our cancer diagnoses: follow the WCRF/AICR recommendations, if you can.

Following these guidelines has been proven to reduce breast cancer (Harris *et al*., 2016). These guidelines are intended to lower cancer incidence, including breast cancer by guiding people of various ethnicities and geographical areas to maintain a healthy weight and to adopt healthy patterns of eating, drinking and physical activity throughout life (WCRF/AICR, 2018). **Therefore, emphasize should be to include a variety of healthy foods, rich in nutrients in one's diet, rather than focusing on one or two single foods.**

Soybeans and Isoflavones

Soy products

Different soy products derived from the soybean includes Edamame, soybean sprouts, soynuts (soaked soybeans), soybean flours, soybean oil, soybean meals, soymilk (lactose and cholesterol free), Tofu (coagulated soy protein curd), Okara (residual solids from soymilk extraction), Natto (fermented soybean with strains of Bacillus subtillis natto), Tempeh (fermented soybean loaf), Miso (fermented rice and soybean with a mixture of molds, yeast and bacteria), soy sauce (seasoning), soy protein isolate (90% protein content), texturized meat alternatives (soy and other vegetable proteins processed into texturized meat substitutes) cheese and dairy alternatives, soy yoghurt, nondairy desserts (soy based ice cream, chipped cream) and nutritional supplements (nutraceutical supplement products like Vit E, Lecithin and Isoflavone) (He & Chen, 2013).

Composition of soybeans, and where isoflavones fit in

Soybeans comprises mostly out of proteins, soybean oil and carbohydrates but also contains other healthy components like phytoestrogens (He & Chen, 2013). Isoflavones are the Phytoestrogen present in soybeans and is further known as a subclass of flavonoids that belongs to plant based polyphenols (Anderson *et al*., 1995). Even though other legumes also contain isoflavones, soybeans contain the highest concentration of isoflavones (Kaufman *et al*., 1997).

Isoflavones and BrCa risk

Isoflavones and increase BrCa risk

Limited number of studies have indicated that isoflavones (genistein) could increase breast cancer risk, however, most of these were in vitro and in vivo models (Seo *et al*., 2006; Limer *et al*., 2006; Isoda *et al*., 2002). There **is no strong evidence in human studies** that suggest an increased risk between soy consumption and breast cancer in pre- or postmenopausal woman (Murkes *et al*, 2011; Johnson *et al*, 2016; Pabich & Materska; 2019).

Isoflavones and prevention of BrCa risk

Results of systematic reviews reporting on the relationship between soy intake and breast cancer risk underlines the fact that no consensus have been reached as yet. Some studies indicate that high consumption of soy may be associated with a decreased risk of breast cancer in Asian populations but not in Western populations. Other factors that may influence results such as the type of soy and study design may influence the overall results (Trock *et al*; 2006; Dong & Qin, 2011; Chen *et al*., 2014; Bahrom & Idris, 2016).

Differences in isoflavone metabolism and components in diverse populations.

According to Yuang *et al*. (2007), the clinical effectiveness of soy isoflavones may be associated with the ability to biotransform soy isoflavones to equol.

Previously, different metabolic rates of isoflavones (genistein and daidzein) were reported between Asian and US Caucasian populations. A 30%-50% rate of the general US population were able to metabolize isoflavones (diadzein) to equol while only 25% to 35% of the US Caucasian population could metabolize isoflavones (He & Chen, 2013). However, 40%-60% of the Asian population (in high soy consumption areas) were able to covert isoflavones (diadzein) to equol. Hispanic and Latino women are also more likely to produce equol (He & Chen, 2013). Thus, end-products of microbial transformations of isoflavones are subjected to extensive individual variations as intestinal bacteria may increase or compromise the biological activity of dietary isoflavones (production of equol).

Additionally, it was formerly reported that the isoflavone content (total diadzein/diadzin, genistin/genestein, glycetin/glycitein depending on the glycoside conjugation or aglycone forms) in soybeans differ among cultivars and geographical locations (see Table 1) (Wang & Murphy, 1994; Kim *et al*., 2005; Seguin *et al*., 2004; Sertovic *et al*., 2012).

Table 1. Content of isoflavones: diadzein, genestein and glycitein in different geographical areas.

Country	Daidzein Mean + SD (mg/100g raw soybean)	Genestein Mean + SD (mg/100g raw soybean)	Glycitein Mean + SD (mg/100g raw soybean)	Total Isoflavone content range
Australia	39.88±16.98	65.64±19.35	17.12±4.10	120.84±34.12
Brazil	29.09±12.70	67.57±13.69	13.10±3.58	99.82±21.22
China	53.33±13.89	57.98±5.60	11.71±2.35	118.28±21.20
Romania	45.44±10.54	39.78±14.46	22.37±8.19	103.56±18.71
Japan	45.95±22.47	74.33±23.56	9.01±3.21	130.65±41.17
Korea	78.86±19.72	89.32±24.68	18.76±7.13	178.81±47.16
Taiwan	22.77±18.10	45.88±16.78	13.24±5.17	85.68±33.42
United States	61.33±21.48	86.33±20.30	13.33±8.89	159.98±43.58

It is also reported that dietary isoflavonoids consumption differ geographically (Ziaei & Halaby, 2017). The mean daily consumption of isoflavones was reported to be 30mg to 50mg among older particpants in a study conducted in Japan (Messina *et al*., 2006) whilst studies in the US and Europe reported less than 3mg consumption of isoflavones per day (Bai *et al*., 2014; Rizzo *et al.*, 2013). Variuos reports indicate that the incidence of breast cancer is significantly lower in Asian individuals compared with other populations due to the higher consumption of isoflavones in their regular diet (Mense *et al*., 2008; Miller & Snyder, 2012)

High variability in equol production may be due to inter-individual differences in intestinal microflora composition and may play important roles in preventative mechanisms of isoflavones (Yuan *et al*., 2007; He & Chen, 2013). The different rate of metabolic equol production and different isoflavones content of soybeans may partially explain the different effects reported for soy and soy food consumption in Asian populations compared to other European and US populations (Ziaei & Halaby, 2017). He and Chen (2013) further states that the Chinese population could have a possible genetic profile that differs from other populations that are relatively new to soybean consumption. This is due to the fact that soybeans were discovered by the Chinese population more than 5000 years ago and that they may have had an advantage in developing intestinal microflora for optimal digesting and extracting nutrients from soybeans (He & Chen, 2013).

Furthermore, intake of dietary soy during early stages of life (especially during puberty) may provide protection against breast cancer risk (Shu *et al*., 2001; Wu *et al*., 2002) and may partially explain why women who only start consuming soy later in life, lack the chemoprotective effects observed in Asian women (Hilakivi-Clarke *et al*., 1999; Fritz *et al*., 1998).

Conclusion (Take home message)

There is no strong evidence that dietary soy intake is a risk factor for breast cancer.

A number of factors contribute to whether or not soybeans and other soy products may protect against breast cancer in a specific population or geographical area. Given I) the lack of research on this topic in African countries and II) the lack of recommendations by the CUP report on isoflavones, which is the strongest evidence based tool for cancer prevention and survival, no dietary soy intake recommendations in relation to breast cancer risk can be made to African populations.

Emphasize should rather be drawn to maintaining a healthy body weight (postmenopausal), to be physically active and to follow a diet based on variety of healthy, nutrient dense foods.

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