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# Serum levels of IGF-I and BRCA penetrance: a case control study in breast cancer families

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**Abstract** High serum levels of insulin-like growth factor I (IGF-I) are associated with an increased risk of sporadic breast cancer (BC). The aim of the present work is to evaluate the association between IGF-I and hereditary BC risk, using a case–control approach. The work represents an "*ad interim*" cross-sectional analysis of an ongoing study with a prospective design whose aim is to recruit a cohort of women belonging to high genetic risk families to test potential modulators of penetrance and prognosis. The *odd* of exposure to high serum IGF-I levels among women with a previous diagnosis of BC ("cases") was compared with the *odd* among unaffected "controls". The odds ratio (OR) and 95% confidence intervals (CIs) were estimated by unconditional logistic regression, controlling for confounders. We analysed 308 women (209 cases and 99 controls) at high genetic risk of BC. The adjusted OR of BC for the upper tertile of serum IGF-I *versus* the lowest one was 3.5 (95%CI 1.4–8.8). Excluding from the analysis 64 women under current Tamoxifen or GnRH analogues treatment, the adjusted OR of BC became 3.7 (95%CI 1.4–9.9). The association became stronger restricting the analysis to the 161 women (97 cases and 64 controls) with a proven *BRCA* mutation. If confirmed by a prospective approach, the association between IGF-I and familial BC will open further options for reducing BC risk in susceptible women.

**Keywords** IGF-I · *BRCA* genes · Penetrance · Breast cancer · Primary prevention

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## Introduction

High serum levels of insulin-like growth factor I (IGF-I) are associated with an increased risk of breast cancer (BC) [1, 2]. The first published studies suggested that the association of IGF-I and BC was confined to young pre-menopausal women. Subsequent studies, however, found similar associations after menopause.

The IGF pathway comprises a complex system of molecules involved in regulation of different biological functions [1]. IGF-I is essential for the normal development of the female breast both during puberty and pregnancy [3], regulates cell proliferation and apoptosis [4] and is functionally linked to angiogenic factors and BC progression [5]. Growth hormone (GH) is the main regulator of IGF-I levels in the blood and the biological activity of IGF-I is modulated by the IGF-I binding proteins (IGFBPs) [6], two of which, IGFBP1 and IGFBP2 are synthesised in the liver under the control of insulin. Insulin promotes the synthesis of IGF-I [7] and inhibits IGFBPs formation in the liver [8],

thus increasing the bio-availability of IGF-I. Insulin improves also the synthesis of androgens in the ovary and inhibits liver production of the sex hormone binding globulin (SHBG), thus increasing the bio-availability of sex steroids (both androgens and estrogens) [8] consistently recognised as major risk factor for pre and post-menopausal BC [9–13]. Estrogens and IGF-I cooperates for the proliferation of BC cells [14].

Up to 5% of BC and 10% of ovarian cancer (OC) may be associated with an autosomic dominant *BRCA* gene mutations [15]. Such mutations confer very high lifetime risks of developing BC and most BC cases occur at young ages. Estimates of the lifetime cumulative risk (penetrance) of BC associated with *BRCA* mutations range from about 80% in studies on high risk families [16–20], to around 45% in population-based studies [21–27]. A sizeable proportion of mutation carriers, however, do not develop BC at all or develop it only late in life. Therefore, the penetrance of the genetic trait may be regulated through other genetic or environmental factors such as dietary, metabolic, and growth factors.

A case–control study within a cohort of 80 French-Canadian BC families showed that high energy intake (that is usually associated with higher bio-availability of growth factors) was positively and significantly associated with BC risk in *BRCA* mutation carriers [28]. A case-only study (COS), on gene-environment interaction in the occurrence of BC before the age of 40 [29–31] suggested a positive significant association with high consumption of milk in Italian women with a high probability of *BRCA* mutation [30]. Milk, directly stimulates insulin production or release [32, 33] and its consumption is associated with higher plasma levels of insulin-like growth factor-I (IGF-I) [34, 35]. Recently, a mechanistic study by Maor et al. [36] hypothesized a functional interaction between the *BRCA*1 and IGF-I systems relevant to breast cancer biology and showed that *BRCA*1 gene expression is regulated by the IGF-I signalling pathway. The same author [37] showed that primary BC related to *BRCA*1 gene mutation revealed a significant elevation in IGF-I receptor levels compared with non-carriers. Another mechanistic study [38] suggested an increased intratumoral IGF-I protein expression in *BRCA* mutation carriers.

We hypothesised, therefore, that IGF-I might be important in hereditary BC. The aim of the present work is to evaluate the association between serum levels of IGF-I and hereditary BC risk, using a case–control approach. The work represents a cross-sectional "*ad interim*" analysis of a larger study with a prospective design who aims to recruit a cohort of women belonging to high genetic risk families to test if IGF-I and other metabolic indicators may influence their risk of BC and BC relapses. Confirming a positive association with BC would help to develop primary prevention recommendations for high risk families.

## Subjects and methods

### Subjects

Eligible study subjects were women with or without BC, aged 18–75, with a proved deleterious *BRCA* mutation or belonging to a family with a high probability of harbouring a *BRCA* deleterious mutation (≥50%) estimated on the basis of the family history.

We defined as cases women with a previous invasive BC, whatever their date of diagnosis, and as controls women who had not developed BC. Cases and controls could not be matched by family because several families provided only cases. On the other hand, several families provided only controls because no cases was still alive. All controls, however, were first degree relatives of BC cases.

Healthy women who tested negative for the *BRCA* mutation detected in their family were not eligible. Cases with distant metastases were not eligible.

308 eligible women were recruited through the genetic counselling activity of family clinics of several Italian Cancer Institutes.

The study was supported by the Italian Ministry of Health and the Italian League Against Cancer and was approved by the Institutional Review Board and Ethical Committee of the collaborating Cancer Institutes.

All participants received full information about the study, and provided a written consent. They were enquired about their family history of breast and ovarian cancer with genetic pedigree reconstruction (to compute probability of *BRCA* mutation) and, if one or more family members had been tested for *BRCA1* or *BRCA2* deleterious mutation, about the results of the test.

Participants were invited to undergo an anthropometric visit, to donate a blood sample and to fill in a questionnaire enquiring data about all factors related both to familial BC and hormonal-metabolic factors under study (disease treatment, oral contraceptive use, reproductive factors). Body weight was measured using electronic scale with women in light clothes and without shoes.

### Methods

#### *Software to compute probability of mutation*

The major requirement of this study on hereditary BC was the identification of women at high genetic risk of BC. Without genetic test, the probability of a *BRCA* deleterious mutation was computed using a software developed in the frame of a multinational case-only study (C.O.S.) [29–31]. The C.O.S. software, based on the Bayesian logic developed by Berry and Parmigiani [39, 40], requires sex, age or age at death, age at BC or ovarian cancer diagnosis, and

age of diagnosis of second or contralateral BC, in each participant's family member and can accommodate up to the 4th degree relatives. It requires as well assumptions about the incidence of BC and OC in the general population and in *BRCA* mutation carriers. Since BC incidence has increased over generations, both in the general population [41] and in mutation carriers [42–45], we estimated age and birth cohort-specific BC incidence and penetrance rates [31, 46, 47]. Software results compare favourably with respect to the more widely used BRCAPRO [48].

*Laboratory measurements*

Blood samples were collected at recruitment into the study. Women were requested to donate 15 ml of blood; serum samples were aliquoted and stored at $-80^{\circ}$.

Serum IGF-I was measured using commercially-available radioimmunoassay kits from Biosource (nivelles, Belgium). The coefficients of intra- and inter-assay variation were, respectively: 2.8 and 5.3% for a mean IGF-I level of 304 ng/ml.

The technicians analyzing the serum samples were blinded to the case or control status of the patients.

*Statistical methods*

The statistical analysis aimed to test the association between IGF-I and BC in women at high genetic risk. According to a case–control methodology the *odd* of exposure to high IGF-I levels among women with a previous diagnosis of BC ("cases") was compared with the *odd* among unaffected "controls".

IGF-I levels were normally distributed; we defined IGF-I tertiles on the basis control population.

The means of continuous variables in affected women were compared with those of unaffected by using Student's *t* test. Chi-squared test was used to compare frequencies and percentages in relation to the disease status. An unconditional logistic regression model was used to compute the *odds ratios* (ORs) and 95% confidence intervals (CIs); the dichotomous dependent variable was women's disease status. The following covariates were considered as potential confounders according to a priori hypotheses: centre, age (in quintiles), body mass index (BMI) (in quintiles) menstrual status (natural menopause, induced menopause, first, second, third and fourth week of menstrual cycle, irregular cycle), fasting (yes or no) and time at blood test ($\leq$10:00, 10:01–12:00, >12:00).

As hormonal treatment for BC is known to reduce IGF-I levels we carried out an analysis restricted to women without current hormonal treatment [49].

We performed also an analysis restricted to *BRCA* mutation carriers.

As time elapsed since BC diagnosis was associated with IGF-I levels, we carried out an analysis excluding cases diagnosed 10 years or more before recruitment.

A *P*-value of $<0.05$ was taken to be significant. All statistical tests were two-sided. All analysis were performed using the STATA 11 statistical package.

## Results

The analysis was carried out on 308 women (mean age 45.0 $\pm$ 10.6 standard deviation), 209 cases and 99 controls. 161 of them, 97 cases and 64 controls (mean age 46.2 $\pm$ 11.2 standard deviation), tested positive for a *BRCA* gene mutation. 92 cases and 35 controls were not tested but belonged to a family with a probability of mutation over 50%. 20 cases who tested negative for *BRCA1* and *BRCA2* deleterious mutations were also included in the main analysis because their "a priori" probability of mutation was over 50% and the genetic test may lack sensitivity.

Cases were diagnosed on average 7.1 years (standard deviation 6.3) before recruitment.

Relevant characteristics of cases and controls, are reported in Table 1. BC cases were significantly older than controls. They showed a significantly different menstrual status, with a higher frequency of iatrogenic menopause. Cases showed a significantly lower weight than controls ($P = 0.02$) but there were no statistically significant differences in mean height and BMI. Oral contraceptive had been used by 63.5% of cases and by 61.6% of controls. 55 cases and only one control (a women with a positive genetic test) was under current Tamoxifen treatment.

The distribution of serum levels of IGF-I according to the disease status and potential confounding variables is reported in Table 2.

IGF-I significantly decreased with age. As a consequence, BC cases had somewhat lower average serum levels of IGF-I than controls (177.4 $\pm$ 61.0 ng/ml *versus* 192.8 $\pm$ 78.8 ng/ml, $P = 0.06$). However, post-menopausal BC cases, both with natural and induced menopause, showed significantly higher serum levels of IGF-I than post-menopausal controls ($P = 0.05$ and $P = 0.04$). In both cases and controls, IGF-I increased during the first 3 weeks of menstrual cycle and decreased during the fourth. Cases under Tamoxifen treatment had significantly lower IGF-I levels than cases without treatment ($P = 0.00$). Cases under GnRH analogues treatment had a non significantly higher IGF-I levels than cases without treatment ($P = 0.08$). Among cases IGFI levels initially increased by increasing BMI but decreased in overweight women. We did not find any significant association between serum levels of IGFI and type of *BRCA* mutation

**Table 1** Distribution of characteristics under study in cases and controls

| | Cases (209) | Controls (99) | P* |
|---|---|---|---|
| Age mean ± standard deviation (SD) | 47.2 ± 9.4 | 40.3 ± 11.5 | **0.00** |
| Height (cm) mean ± SD | 162.5 ± 6.3 | 163.2 ± 5.8 | 0.34 |
| Weight (Kg) mean ± SD | 62.6 ± 9.8 | 65.8 ± 13.9 | **0.02** |
| BMI (Kg/m$^2$) mean ± SD | 23.7 ± 3.9 | 24.8 ± 5.3 | 0.06 |
| Oral contraceptive | | | |
| % never | 36.5 | 38.4 | 0.75 |
| Ever | 63.5 | 61.6 | |
| Menstrual status | | | |
| % natural menopause | 14.3 | 15.2 | **0.00** |
| Induced menopause | 58.4 | 6.1 | |
| % 1 week of cycle | 5.3 | 13.1 | |
| 2 week of cycle | 4.3 | 18.2 | |
| 3 week of cycle | 8.6 | 23.2 | |
| 4 week of cycle | 6.7 | 18.2 | |
| Irregular cycle | 2.4 | 6.0 | |
| Fasting | | | |
| % yes | 63.7 | 67.7 | 0.89 |
| No | 36.3 | 32.3 | |
| Time at blood test | | | |
| % ≤ 10:00 | 9.6 | 7.1 | 0.67 |
| 10:01-12:00 | 23.0 | 26.2 | |
| > 12:00 | 67.4 | 66.7 | |
| Tamoxifen treatment** | | | |
| % never | 47.1 | 99.0 | **0.00** |
| Current use | 25.0 | 1.0 | |
| Past use | 27.9 | 0.0 | |
| GnRH analogues treatment | | | |
| % never | 68.7 | 100.0 | **0.00** |
| Current use | 15.4 | 0.0 | |
| Past use | 15.9 | 0.0 | |
| Genetic test | | | |
| % BRCA 1 | 29.7 | 38.3 | **0.00** |
| % BRCA 2 | 16.8 | 26.3 | |
| % Negative Test | 9.5 | 0.0 | |
| % Not tested | 44.0 | 35.4 | |

Bold values indicate $P < 0.05$

* $P$ of differences using Student's $t$ test for continuous variables and Chi-squared test for frequencies and percentages comparison

** One single control was under current Tamoxifen treatment

or probability of *BRCA* mutation (data not shown). There was no significant association with fasting conditions ($P = 0.89$).

We examined the association between serum levels of IGF-I and hereditary BC by a multiple logistic regression model (Table 3). The adjusted OR of BC for the upper tertile of serum IGF-I *versus* the lowest one was 3.5 (95%CI 1.4–8.8) with a significant trend of increased risk with increasing IGF-I concentration ($P = 0.01$). Excluding from the analysis 64 women under current Tamoxifen and/or GnRH analogues treatment, the adjusted OR of BC became 3.7 (95%CI 1.4–9.9) comparing the upper *versus* lowest tertile of IGF-I (Table 3a).

Restricting the analysis to the 161 women with a proved *BRCA* mutation (Table 3b), the adjusted OR of BC for the upper tertile of serum IGF-I *versus* the lowest one was 7.0 (95% IC 1.4-35.6). Excluding 25 women under current Tamoxifen and/or GnRH analogues treatment the OR became 6.6 (95% IC 1.3–34.2) ($P$ for trend 0.02). A separated analysis for *BRCA1* and *BRCA2* mutated women did not suggest a differential effect (data not shown).

Among the 147 women (112 cases and 35 controls) included in the study because a high probability of *BRCA* mutation, but without a positive test, the adjusted OR of BC for the upper tertile of serum IGF-I *versus* the lowest one was 2.2 (95%CI 0.5–10.2) (Table 3c).

Excluding 71 cases diagnosed 10 years or more before enrollment into the study the association of IGF-I with BC became stronger. The adjusted OR of BC for the upper tertile of serum IGF-I *versus* the lowest one was 4.2 (95%CI 1.5–11.8; $P$ for trend = 0.00)(data not shown).

## Discussion

Comparing affected *versus* unaffected women belonging to high genetic risk families we found an increased risk of BC associated with high serum levels of IGF-I. This was, however, only an exploratory analysis that needs to be confirmed using a prospective approach. The study in fact, was a cross sectional analysis of baseline IGF-I values in a cohort of women belonging to high risk families who are being followed-up to test if IGF-I may modify the penetrance of genetic susceptibility and influence their risk of BC and of BC relapse.

Few studies tried to study *BRCA* penetrance modulators. Up to now, results on the possible role of several genes related to hormonal and growth factors as potential modifiers of risk (including androgen receptor, *AIB1, HRAS, IGF1,19-CA,* and progesterone receptor) have been inconsistent [50–53]. At present, there are no studies testing the relationship of serum levels of growth factors and penetrance of breast and ovarian cancer in *BRCA* mutation carriers. However, mechanistic studies hypothesized a functional interaction between the *BRCA1* and IGF-I systems relevant to BC biology and showed that *BRCA1* gene

**Table 2** Distribution of serum levels of IGF-I according to the disease status and potential confounding variables

| Quintiles of age (years) | IGF-I (mean ± SD) | | | *P** |
|---|---|---|---|---|
| | Cases | Controls | Total | |
| 1 (18.0–36.6) | 209.8 ± 50.0 | 226.3 ± 83.0 | 220.2 ± 72.6 | |
| 2 (36.7–41.4) | 200.6 ± 54.8 | 192.8 ± 59.7 | 197.5 ± 56.0 | |
| 3 (41.6–46.3) | 196.2 ± 65.4 | 180.6 ± 99.2 | 193.4 ± 71.9 | |
| 4 (46.4–54.1) | 157.8 ± 58.3 | 150.2 ± 57.5 | 156.6 ± 57.8 | |
| 5 (54.3–73.2) | 145.3 ± 45.7 | 139.2 ± 49.6 | 143.7 ± 46.3 | **0.00** |
| *Menstrual status* | | | | |
| Natural menopause | 168.3 ± 55.1 | 136.0 ± 48.2 | 157.6 ± 52.9 | |
| Induced menopause | 170.0 ± 63.7 | 116.3 ± 25.1 | 167.5 ± 63.4 | |
| 1st week of menstrual cycle | 164.7 ± 35.9 | 186.4 ± 66.3 | 176.4 ± 54.5 | |
| 2nd week of menstrual cycle | 187.6 ± 37.9 | 229.9 ± 98.2 | 215.8 ± 84.7 | |
| 3rd week of menstrual cycle | 215.6 ± 46.9 | 226.1 ± 75.6 | 221.5 ± 64.1 | |
| 4th week of menstrual cycle | 215.3 ± 78.5 | 198.0 ± 64.5 | 205.5 ± 70.3 | |
| Irregular cycle | 180.6 ± 23.7 | 170.0 ± 65.1 | 174.8 ± 48.7 | **0.00** |
| *Time at blood test* | | | | |
| ≤10:00 | 170.0 ± 63.6 | 176.5 ± 83.2 | 171.7 ± 67.5 | |
| 10:01–12:00 | 180.2 ± 52.8 | 203 ± 75.3 | 188.3 ± 62.1 | |
| >12:00 | 177.5 ± 63.4 | 190.4 ± 80.4 | 181.6 ± 69.4 | 0.68 |
| *Fasting* | | | | |
| Yes | 181.7 ± 60.2 | 186.3 ± 60.2 | 183.1 ± 59.5 | |
| No | 174.9 ± 61.8 | 195.8 ± 86.5 | 182.0 ± 71.5 | 0.89 |
| *Current Tamoxifen treatment* | | | | |
| Yes | 153.0 ± 44.8 | Not applicable | | |
| No | 190.7 ± 63.1 | | | **0.00** |
| *Current GnRH treatment* | | | | |
| Yes | 195.4 ± 58.5 | Not applicable | | |
| No | 175.1 ± 59.7 | | | 0.08 |
| *BMI* | | | | |
| 1 (17.4–20.6) | 174.8 ± 50.2 | 199.0 ± 68.9 | 184.2 ± 58.8 | |
| 2 (20.7–22.1) | 174.2 ± 65.3 | 182.9 ± 57.9 | 176.4 ± 63.1 | |
| 3 (22.2–24.1) | 187.8 ± 64.5 | 169.9 ± 60.4 | 183.4 ± 62.9 | |
| 4 (24.2–26.6) | 183.7 ± 61.1 | 229.7 ± 107.6 | 197.1 ± 79.4 | |
| 5 (26.7–42.6) | 162.9 ± 60.7 | 180.5 ± 80.4 | 170.4 ± 69.7 | 0.06 |

Bold values indicate $P < 0.05$

*$t$ test for total population

expression is regulated by the IGF-I signalling pathway [36–38]. Our results support this hypothesis and suggest that serum levels of IGF-I may be a risk factor for hereditary BC. The greatest OR was found restricting the analysis to women with a positive *BRCA* genetic test.

There are several limitations to our study. First, we included prevalent cases from families with several BC survivors. Since we collected data and blood samples from our BC cases an average of 7.1 years after diagnosis, any relationship between serum levels of IGF-I and tumour-specific survival may have resulted in a biased estimate of the odds ratio. High IGF-I levels, in fact, may confer an increased risk of recurrences [54], which would reduce the prevalence of high levels in the selected series of cases. This bias might have reduced the strength of the association. Moreover, we found that serum levels of IGF-I decreased by increasing time from BC diagnosis (data not shown), which was only partially explained by increasing age, suggesting that patients with low levels of IGF-I experienced longer survival. Consistently our sensitivity analysis showed increasing ORs excluding cases diagnosed in the distant past.

Second, given the cross-sectional design, serum parameters of BC cases may be affected by disease treatment. Actually, Tamoxifen reduced the IGF-I levels, thus causing

**Table 3** Adjusted ORs and 95% CIs for tertiles of serum levels of IGF-I

| | | | | *P* for trend |
|---|---|---|---|---|
| (a) All participants (308 women) | | | | |
| Tertiles of serum IGF-I (ng/ml) | 1° 41.4–154.0 | 2° 159–207.5 | 3° 215.1–524.5 | |
| All participants (209 cases and 99 controls) | 1 | 2.5 (1.0–5.6) | 3.5 (1.4–8.8) | 0.01 |
| Excluding current Tamoxifen and GnRH analogues users (146 cases and 98 controls) | 1 | 2.8 (1.2–6.5) | 3. 7 (1.4–9.9) | 0.01 |
| (b) Participants with positive genetic test only (161 women) | | | | |
| Tertiles of serum IGF-I (ng/ml) | 1° 47.6–146.6 | 2° 154–200.9 | 3° 203.6–405.5 | |
| All mutation carriers (97 cases and 64 controls) | 1 | 4.7 (1.3–17.3) | 7.0 (1.4-35.6) | 0.02 |
| Excluding current Tamoxifen and GnRH analogues users (73 cases and 63 controls) | 1 | 5.2 (1.3–20.6) | 6.6 (1.3–34.2) | 0.02 |
| (c) Participants belonging to a family with a high probability of harbouring a *BRCA* deleterious mutation (147 women) | | | | |
| Tertiles of serum IGF-I (ng/ml) | 1° 41.4–168.6 | 2° 171–222.5 | 3° 230.2–524.5 | |
| All women (112 cases and 35 controls) | 1 | 1.5 (0.4–6.0) | 2.2 (0.5–10.2) | 0.33 |

OR adjusted for age, centre, menstrual status, BMI, fasting and time at blood test

an underestimation of the OR. The treatment with GnRH analogues was associated with higher IGF-I levels. This latter observation was unknown "a priori" and may have occurred by chance. Previous observations, in fact, showed that GnRH analogues treatment did not change IGF-I levels in prostate cancer patients [55] and decreased levels of free IGF-I in children with central precocious puberty [56]. We checked, however the effect of excluding only cases under hormonal treatment without substantially any significant change in the strength of the association. Finally, since BC is a frequent disease in *BRCA* mutation carriers, the OR is not a reliable estimate of the relative risk. Given the expected cumulative incidence of BC in mutation carriers at the age of our cases (about 10%) [57] one can estimate that an OR = 3.5 could reflect a relative risk of 3.1. This overestimate, however, does not affect the statistical significance of the results. Overall the potential biases discussed above do not seem having caused any major overestimation of the observed OR. However, given the wide confidence intervals, larger studies are necessary to confirm or refute this observation. We expect that our ongoing prospective study will be more informative but we also expect that its statistical power will be affected by the increasing frequency of prophylactic mastectomy and adnexiectomy.

Knowledge of BC susceptibility genes, along with the introduction of predictive genetic testing, has made it possible to identify women at increased risk for inherited breast and ovarian cancer. Options currently available for these women include surveillance programs aimed at BC early detection, risk reducing bilateral mastectomy, and prophylactic adnexiectomy, while non-surgical primary prevention options (e.g. chemo-preventive options for interrupting the oestrogen-signalling pathway) are promising, but not yet firmly established [58, 59]. Tamoxifen adjuvant treatment has been found associated with lower incidence of contralateral BC in *BRCA* positive patients [60, 61]. Tamoxifen, however, seems equally effective in *BRCA2* patients (mostly estrogen receptor positive) as in *BRCA1* patients (mostly estrogen receptor negative), suggesting that the preventive mechanism may be partially mediated through the lowering effect on IGF-I levels. Several epidemiological observation suggested that factors related to bioavailability of growth factor, such as diet [62], body weight [63], high energy intake [63], and physical activity [64] may affect the penetrance in *BRCA* mutation carriers and in women belonging to high genetic risk families. The present results suggest that a mechanism underlying these associations may be the increased levels of IGF-I. We know that all these factors are related to the hormonal and metabolic risk pattern that is relevant for sporadic BC aetiology and prognosis and may be potentially modified [65]. A long-term low-protein and low calories diet is associated with lower insulin and IGF-I levels [66]. Recently, also physical activity has been found associated with lower IGF-I levels [67]. We previously showed that in post-menopausal women a comprehensive change in diet with reduced consumption of refined carbohydrates and saturated fats and increased consumption of whole-grain cereals, pulses and vegetables can reduce insulin and sex hormones, and increase the IGF-I binding proteins 1 and 2 thus reducing the bioavailability of IGF-I [68–71]. Confirming the associations between IGF-I and other markers of insulin resistance and familial BC in a prospective cohort of a large series of participants, susceptible women will have further options for reducing their risk of BC, either through lifestyle or chemoprevention.

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