Diabetes risk reduction diet and the risk of breast cancer

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Objective Diabetes and insulin levels may increase the risk of postmenopausal breast cancer. In the present investigation, we aimed at evaluating whether adherence to a diabetes risk reduction diet (DRRD) lowers the risk of breast cancer.

Methods We used data from an Italian, multicentric case-control study (1991–1994) including 2569 incident histologically-confirmed breast cancer cases and 2588 hospital controls. A food frequency questionnaire collected subjects' usual diet. We derived a DRRD score on the basis of eight items: intake of cereal fiber, total fruit, coffee, polyunsaturated to saturated fats ratio and nuts (higher scores for higher intakes), and dietary glycemic index, red/processed meat and sugar-sweetened beverages/fruit juices (higher scores for lower intakes). The score theoretically ranged 8–37, with higher values indicating greater DRRD adherence. Odds ratios (ORs) of breast cancer according to the DRRD score were estimated using multiple logistic regression models.

Results The DRRD score was inversely related to the risk of breast cancer. The ORs were 0.93 [95% confidence interval (CI), 0.89–0.98] for a three-point score increment and 0.76 (95% CI, 0.64–0.89) for the highest versus the lowest quartile (*P* for trend 0.001). Inverse associations were observed in subgroups of covariates.

Conclusions Higher DRRD adherence may decrease the risk of breast cancer. *European Journal of Cancer Prevention* 31: 339–345 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Type II diabetes has been associated to a modest increased risk of postmenopausal breast cancer in several studies. Diabetic subjects have a 10–30% excess risk of postmenopausal breast cancer, likely explained by residual confounding by adiposity (La Vecchia *et al.*, 2011; Boyle *et al.*, 2012), a predisposing factor of both type II diabetes (Carey *et al.*, 1997) and postmenopausal breast cancer (Chan *et al.*, 2019; van den Brandt *et al.*, 2021). In premenopause, diabetes is not associated with breast cancer (Boyle *et al.*, 2012) and high BMI decreases the risk (van den Brandt *et al.*, 2021). Studies linking hallmark features of type II diabetes such as hyperglycemia, hyperinsulinemia and insulin resistance with breast cancer yielded mixed findings, suggesting direct as well as null associations (Hernandez *et al.*, 2014). Higher plasma levels of insulin-like growth factor-1 (IGF-1) may increase the risk of breast cancer, but, again, the evidence is not clear-cut (Schernhammer *et al.*, 2006; Key *et al.*, 2010).

Insulin increases sex hormones and decreases sex hormone-binding globulin, which results in increased plasma-free steroid hormones concentrations, free estrogens in particular (Wolf *et al.*, 2005). High levels of endogenous sex hormones are associated with an excess risk of postmenopausal breast cancer (Key *et al.*, 2002). In addition, hyperinsulinemia secondary to insulin resistance may stimulate cellular signaling pathways with a role in tumorigenesis, including the AKT and extracellular-signal-regulated-kinase (ERK) pathways (Wolf *et al.*, 2005), and may increase IGF-1 expression, which is involved in the etiology and progression of cancer (Gallagher and LeRoith, 2010). A role of hyperglycemia and inflammatory cytokines has also been suggested (Giovannucci *et al.*, 2010).

Selected aspects of diet may have a certain role on breast cancer. Some specific dietary factors have been related to the disease, including alcohol and red and processed meat (Inoue-Choi *et al.*, 2016; Farvid *et al.*, 2018) among

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the unfavorable factors, and fruit and nonstarchy vegetables (Farvid *et al.*, 2016; Farvid *et al.*, 2019), dietary fiber (Farvid *et al.*, 2020) and carotenoids (Eliassen *et al.*, 2012) among the favorable ones; however, except for alcohol (Bagnardi *et al.*, 2015), evidence remains controversial. In addition, healthy dietary patterns considering simultaneously multiple aspects of diet, including the Mediterranean diet (Buckland *et al.*, 2013; Turati *et al.*, 2018) and a diet compliant with the nutritional recommendations from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) (Turati *et al.*, 2020), have been associated to a reduced risk of breast cancer (Xiao *et al.*, 2019).

A dietary pattern developed for diabetes risk reduction [diabetes risk reduction diet (DRRD)] (Rhee *et al.*, 2015) characterized by high intakes of cereal fiber, coffee, fruit and nuts, a high ratio of polyunsaturated to saturated fats, and low dietary glycemic index (GI), low intakes of red/processed meat, sugar-sweetened beverages/fruit juices and trans fats showed a modest inverse association with the risk of breast cancer in a pooled analysis of two large US cohorts (Kang *et al.*, 2020). Further data are needed to clarify the issue.

In the current investigation, we evaluated whether a score measuring adherence to the DRRD lowers the risk of breast cancer using data from a large, multicentric case-control study conducted in a Mediterranean country.

Methods

We used data from a multicentric case-control study on breast cancer conducted from June 1991 to April 1994 in six Italian areas: the provinces of Pordenone and Gorizia, the greater Milan area, the urban area of Genoa, the province of Forli, the province of Latina, and the urban area of Naples (Franceschi *et al.*, 1995).

Cases were 2569 women with incident, histologically-confirmed breast cancer (median age 55, range 23–74 years) admitted to major teaching and general hospitals of the study areas. Controls were 2588 women (median age 56, range 20–74 years) with no history of cancer admitted to the same hospitals for acute, non-neoplastic, nongynecological conditions, unrelated to hormonal or digestive tract diseases or to dietary-related conditions. Among controls, 22% were admitted for traumas, 33% for other orthopedic diseases, 15% for acute surgical conditions, 18% for eye diseases and 12% for other miscellaneous diseases. Less than 4% of cases and controls approached for interview refused to participate. The study was approved by the local ethics committees according to the rules at the time of data collection. All procedures were performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

Cases and controls were interviewed in hospital by centrally trained interviewers, using a standard structured questionnaire. This included information on sociodemographic and anthropometric factors, lifestyle habits, including tobacco smoking, alcohol drinking and physical activity, as well as obstetric, gynecologic and general medical history, and family history of cancer. Subjects' usual diet in the previous 2 years was assessed through a food frequency questionnaire (FFQ). Subjects were asked to indicate their average weekly consumption of 78 food items or food groups. Open questions were used to report foods/recipes eaten at least once a week not included in the FFQ list. The FFQ included also a few questions aiming at assessing fat intake pattern as well as information on salt and garlic use. Intakes lower than once a week, but at least once per month, were coded as 0.5/week. Nutrient and total energy intake were determined using an Italian food composition database (Salvini *et al.*, 1998; Gnagnarella *et al.*, 2004).

We calculated the DRRD score according to Kang *et al.* (2020), on the basis of the following eight dietary components: cereal fiber, coffee (caffeinated and decaffeinated), total fruit, nuts, ratio of polyunsaturated to saturated fats, dietary GI, red and processed meat and sweetened beverages and fruit juices. We assigned a score between 1 and 5 according to quintile of consumption, in ascending order for cereal fiber, coffee, total fruit and ratio of polyunsaturated to saturated fats (i.e. factors associated to low diabetes risk), and in descending order for GI and red/processed meat (i.e. factors associated to high diabetes risk). Quintiles were derived among control women. The consumption of sweetened beverages and fruit juices was low in our population (i.e. 3094 (60%) women did not consume either sweetened beverages or fruit juices regularly); we, therefore, assigned a score of 5 to non-consumers, a value of 3 to women drinking ≤2 drinks per week (i.e. the median value among control drinkers), and a value of 1 to women drinking more than two drinks per week. There was no specific question on nuts consumption in the FFQ; women reporting nuts consumption ($n = 45$) in the open questions of the FFQ were assigned a score of 2; a score of 1 was assigned to the remaining women. Due to the lack of trans fats information within the Italian food composition tables, trans fats intake could not be calculated and included in the score. For each woman, the DRRD score was obtained by summing up the scores in all the dietary components. The score thus theoretically ranged from 8 to 37, with higher values indicating greater adherence to the DRRD.

Statistical analysis

Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) of breast cancer according to approximate quartiles (derived among controls) of the DRRD score and to a three-point increment in the score were estimated using unconditional logistic regression models. Two models were fitted: a first model included terms for study center, age and education; a second model included further terms for year of interview, BMI, physical activity, smoking, history of diabetes, parity, menopausal status and age at menopause, use of oral contraceptives and hormone replacement therapy, family history of breast cancer, alcohol intake and total energy intake. Trends in ORs across score quartiles were evaluated by including an ordinal variable for quartiles in the logistic regression models. A few missing data in the adjustment factors were replaced by the median value (continuous variables) or mode category (categorical variables) according to case/control status. We conducted the following sensitivity analyses: (1) we included in the models the adjustment for total vegetable intake and (2) for weight change since age 30 (the information was not available for 148 women), (3) excluded diabetic women from the analyses and (4) assessed the association between the DRRD score and breast cancer excluding each score component in turn from the DRRD score calculation. Subgroup analyses were performed according to menopausal status, education, parity, BMI and smoking status. Heterogeneity across strata was tested by a likelihood ratio test comparing models with and without interactions terms for the score quartile variables and the subgroup factors.

All the analyses were conducted using the SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

Results

Table 1 gives the distribution of breast cancer cases and controls according to age and selected covariates. Cases were more educated than controls and have more frequently a family history of the disease; they also tended to have lower parity and to report more frequently a history of diabetes.

Table 2 provides the ORs and corresponding 95% CIs of breast cancer according to the DRRD score. The DRRD score was inversely related to the risk of breast cancer. ORs derived from models with minimal adjustment and those derived from models adjusted for several covariates were very similar. Based on the fully adjusted models, the OR for a three-point increment in the score was 0.93 (95% CI, 0.89–0.98), and women in the highest quartile of the DRRD score had a 24% reduced risk of breast cancer (95% CI, 11–36%) compared to those in the lowest quartile.

Further adjustment for total vegetable consumption (OR for a three-point increment in the score: 0.95, 95% CI, 0.90–0.996; OR_{Q4vsQ1}: 0.80, 95% CI, 0.67–0.94) or weight change since age 30 (OR for a three-point increment: 0.93, 95% CI, 0.88–0.97; OR_{Q4vsQ1}: 0.74, 95% CI, 0.62–0.87), as well as the exclusion of diabetic women from the analyses (OR for a three-point increment: 0.93, 95% CI, 0.89–0.98; OR_{Q4vsQ1}: 0.74, 95% CI, 0.63–0.88) did not materially affect any of the results. Fairly consistent results were found after removing each dietary factor in turn from the DRRD score calculation; the ORs for the highest *versus* the lowest score quartile varied between 0.70 (with the exclusion of the cereal fiber component) and 0.85 (of borderline significance, with the exclusion of the dietary GI component or the polyunsaturated:saturated fats component) (Supplementary Information, Supplemental digital content 1, *http://links.lww.com/EJCP/A330*).

Figure 1 shows the results of the subgroup analysis. The inverse association between the DRRD score and breast cancer was observed in all the subgroups examined, being apparently stronger among premenopausal, more educated, nulliparous and ex-smoker women; however, tests for interaction did not reveal significant heterogeneity across all the strata considered.

Table 1 Distribution of 2569 breast cancer cases and 2588 controls by age and other selected covariates (Italy, 1991–1994).

	Cases, *n* (%)	Controls, *n* (%)
Age group (years)		
<40	206 (8.0)	257 (9.9)
40-49	633 (24.6)	512 (19.8)
50-59	809 (31.5)	808 (31.2)
60-69	733 (38.5)	775 (30.0)
≥70	188 (7.3)	236 (9.1)
Education[a] (years)		
<7	1259 (49.3)	1569 (61.2)
7-11	714 (28.0)	642 (25.0)
≥12	582 (22.8)	354 (13.8)
Parity[a]		
Nulliparae	401 (15.6)	380 (14.7)
1	584 (22.8)	494 (19.1)
2	968 (37.7)	909 (35.2)
3	406 (15.8)	489 (18.9)
≥4	207 (8.1)	314 (12.2)
Menopausal status[a]		
Premenopausal	988 (38.5)	843 (32.6)
Postmenopausal	1578 (61.5)	1745 (67.4)
History of diabetes		
No	2452 (95.5)	2489 (96.2)
Yes	117 (4.5)	99 (3.8)

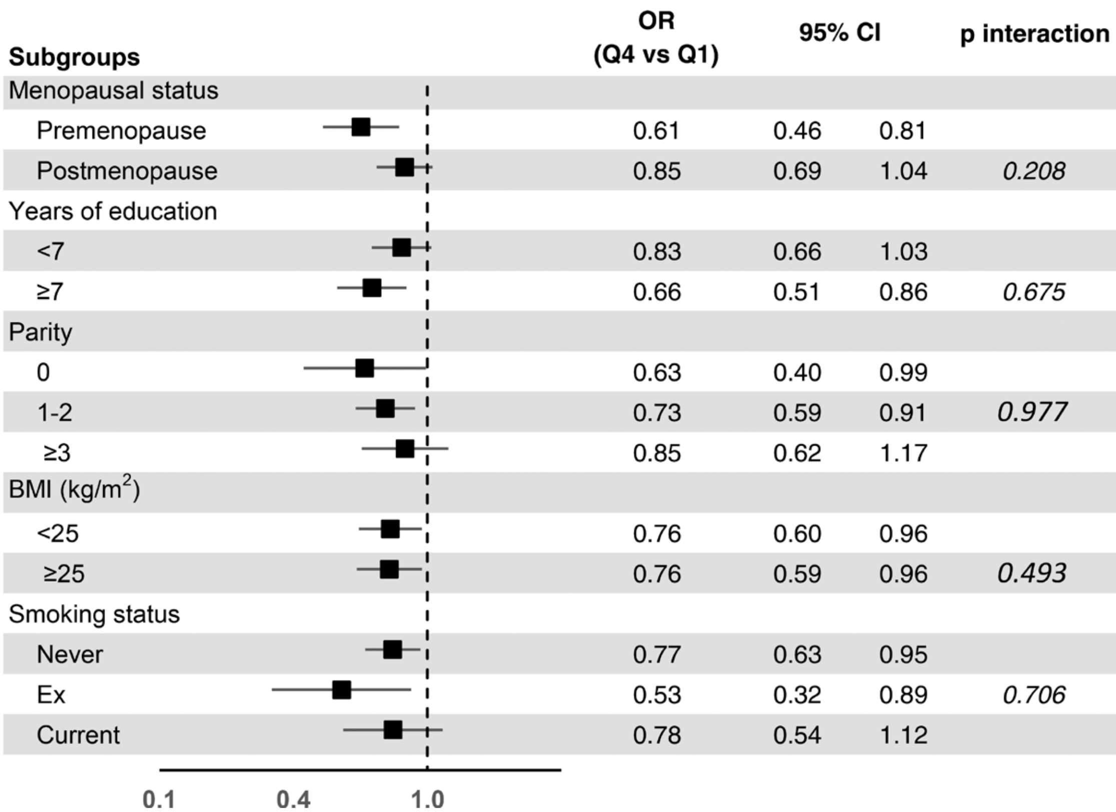
[a]The sum does not add up to the total because of some missing values.

Table 2 Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for 2569 cases of breast cancer and 2588 controls, according to approximate quartiles of the diabetes risk reduction (DRRD) score (Italy, 1992–1994)

	Cases, *N* (%)	Controls, *N* (%)	OR[a] (95% CI)	OR[b] (95% CI)
DRRD score, quartiles				
I (≤20)	706 (27.5)	673 (26.0)	1[c]	1[c]
2 (21-22)	523 (20.4)	516 (19.9)	0.92 (0.78–1.09)	0.96 (0.82–1.14)
3 (23-25)	776 (30.2)	761 (29.4)	0.91 (0.79–1.06)	0.91 (0.78–1.06)
4 (≥26)	564 (22.0)	638 (24.7)	0.77 (0.65–0.90)	0.76 (0.64–0.89)
χ^2 Trend (*P* value)			9.2 (0.002)	10.5 (0.001)
Three-point increment			0.94 (0.90–0.98)	0.93 (0.89–0.98)

[a]Adjusted for study center, age and education.
[b]Further adjusted for year of interview, BMI, physical activity, smoking, history of diabetes, parity, menopausal status and age at menopause, use of oral contraceptives and hormone replacement therapy, family history of breast cancer, alcohol intake and total energy intake.
[c]Reference category.

Fig. 1



Odds ratios (ORs) of breast cancer for the highest (Q4) versus the lowest quartile (Q1) of the diabetes risk reduction diet (DRRD) score, with corresponding 95% confidence intervals (CIs), in selected subgroups (Italy, 1992–1994). The ORs were adjusted for study center, age, education, year of interview, BMI, physical activity, smoking, history of diabetes, parity, menopausal status and age at menopause, use of oral contraceptives and hormone replacement therapy, family history of breast cancer, alcohol intake and total energy intake, unless the covariate was the stratification factor. The lowest DRRD score quartile was the reference category in the analyses. Tests for interaction considered all the four quartiles of the DRRD score.

Discussion

In the present large multicentric study from Italy, a score measuring adherence to a DRRD and based on eight dietary components was significantly inversely related with the risk of breast cancer. After allowance for a number of potential confounders, including BMI and total energy intake, women in the highest score quartile had a 24% reduced risk of breast cancer compared to those in the lowest quartile. The inverse association between the DRRD score and the risk of breast cancer was observed in all the subgroups considered, although it was somehow more evident among premenopausal, more educated, nulliparous and ex-smoker women. In any case, tests for interaction did not detect any significant heterogeneity across strata.

The only other previous study investigating the association of the DRRD with the risk of breast cancer was a pooled analysis of two large US cohort studies (i.e. the Nurses' Health Study NHS, and the NHSII), following 180 000 women for ≥26 years (Kang *et al.*, 2020). The study found a modestly lower breast cancer risk among women in the highest quintile of the DRRD score compared to those in the lowest quintile (multiple-adjusted hazard ratio, HR, 0.89, 95% CI, 0.84–0.95), which was slightly attenuated after adjusting for weight change since age 18 (HR, 0.92, 95% CI, 0.87–0.98). In our study, further adjustment for weight change since age 30 did not impact the results.

In the assessment of the relationship between diet and the risk of chronic diseases, the analysis of dietary patterns represents an alternative and complementary approach to the analysis of individual foods or nutrients (Hu, 2002). Dietary patterns, which capture the consumption of multiple dietary factors, may be more etiologically relevant than the traditional individual foods/nutrients analysis, particularly when only a few individual dietary factors have shown consistent associations with the disease, such as for breast cancer. The DRRD is a dietary pattern specifically developed for the reduction of diabetes risk. Subjects compliant to the DRRD have a high consumption of cereal fiber, coffee, fruit, nuts and a high ratio of polyunsaturated to saturated fats (i.e. factors inversely related to type II diabetes), and low GI, low intake of red/processed meat, sweetened beverages and fruit juices and trans fats (i.e. factors directly associated to type II diabetes). According to a recent meta-analysis of prospective studies, high intake of total fiber was weakly, but significantly, inversely associated with the risk of breast cancer; when investigating different sources of fiber, however, the meta-analysis did not find any association with the intake of cereal fiber (pooled RR for high *versus* low consumption 0.97, 95% CI, 0.93–1.01, based on 10 studies) (Farvid *et al.*, 2020). While some studies suggested a favorable role of high fruit consumption (Farvid *et al.*, 2019), other studies did not find any association (Emaus *et al.*, 2016), or reported inverse associations restricted to selected subtypes of breast cancer defined by hormone receptor status (Jung *et al.*, 2013). In any case, if anything, the association is likely modest (Aune *et al.*, 2012). Nuts consumption was associated with a marginally significant 10% reduced risk of breast cancer in a meta-analysis of six studies (Zhang *et al.*, 2020). Coffee may decrease the risk of postmenopausal breast cancer, but, again, the association is probably modest (Lafranconi *et al.*, 2018). High intakes of saturated and (n-3) polyunsaturated fats may, respectively, increase and decrease the risk of breast cancer, but the evidence is conflicting (Buja *et al.*, 2020). High GI or GL diets are not, or at most only weakly, directly associated with breast cancer (Turati *et al.*, 2019). Some studies indicated an increased risk of breast cancer for high consumption of red and processed meat (Inoue-Choi *et al.*, 2016; Diallo *et al.*, 2018); however, according to recent meta-analyses, only the intake of processed meat, but not of red meat, increases the risk of breast cancer (by 6–9% when consumed in higher amounts) (Anderson *et al.*, 2018; Farvid *et al.*, 2018). The few studies investigating sugary drinks in relation to breast cancer gave conflicting results (Makarem *et al.*, 2018; Chazelas *et al.*, 2019). We did not include the trans fats component in the DRRD score; however, the intake of trans fats does not appear to increase the risk of breast cancer (Anjom-Shoae *et al.*, 2020). Thus, the reduction in the risk of breast cancer for high adherence to the DRRD was evident even though no strong associations were observed for each of the nutritional components of the DRRD score. Biologic interactions may exist between the various dietary factors of the DRRD pattern. In addition, while the effects of individual dietary factors are examined against the background of average risk associated with other dietary exposures, the use of an inclusive dietary score can account for extremes of cumulative exposure, in the absence of other major nutritional effects (Jacques and Tucker, 2001).

Seeds oil is commonly consumed in the USA, where the score was derived, and is a major dietary contributor of polyunsaturated fats in the country. In the Mediterranean area, olive oil (in particular the extra virgin type) is the main source of dietary fat and is a major source of monounsaturated fatty acids (Trichopoulou *et al.*, 2014). Consumption of olive oil has been favorably related to several diseases, including cardiovascular diseases, various neoplasms (including breast cancer) (Pelucchi *et al.*, 2011) and diabetes (Schwingshackl *et al.*, 2017). When we used the ratio of monounsaturated+polyunsaturated to saturated fats (instead of that of polyunsaturated to saturated fats) in the score calculation, we observed similar results for the overall DRRD score (OR for a three-point increment in the score: 0.95, 95% CI, 0.90–0.99; OR for the highest *versus* the lowest score quartile: 0.80, 95% CI, 0.68–0.93).

Given the retrospective design of the study, potential selection and information bias should be considered. However, the exclusion from the control group of patients admitted for chronic and gynecologic conditions or diseases related to diet modifications or known risk factors for breast cancer, the very high participation rate (>95% for both cases and control), the similar catchment areas and interview setting for cases and controls and the lack of awareness in this population of a possible role of diet on breast cancer risk weigh against these biases. In addition, the FFQ was tested for validity and reproducibility with satisfactory results (Franceschi *et al.*, 1993; Decarli *et al.*, 1996). Although we were able to adjust for a number of potential confounding factors, including BMI and total energy intake, some residual confounding cannot be excluded. However, the fact that OR estimates did not change when several additional potential confounders were added to the models argues against major residual confounding. We could not include *trans* fats in the DRRD score, as proposed by Kang *et al.* (2020), as no information on the content of trans fats in Italian foods is available from food composition tables. Trans fats come primarily from industrial sources, by partial hydrogenation of edible oils. The major sources of trans fats are margarine, fried fast foods, and highly industrially processed foods, including packaged snacks and baked products. Compared to other western countries, consumption of highly industrially processed foods is lower in southern European countries, Italy included (Slimani *et al.*, 2009). As for margarine, in our study, only 2.5, 1.2 and 3.9% of women indicated it as the main fat source, respectively, for cooking meat, frying or seasoning pasta.

Conclusion

Our study suggests that higher adherence to a dietary pattern for diabetes risk reduction lowers the risk of breast cancer. It remains unclear whether this is due to a direct effect of such diet on glycemia and related factors (e.g. IGF-1) or to other mechanisms related to the individual components and their combination. The observation that the effect is greater in premenopausal women would at least in part support the latter hypothesis.

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Conflicts of interest
There are no conflicts of interest.

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