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(Article begins on next page)

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Risk of second primary malignancies in women with breast cancer: results from the European Prospective Investigation into Cancer and Nutrition (EPIC).

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Novelty and Impact

At our knowledge this is the first time that a higher risk of second primary cancers after a breast cancer is described using cohort data, with a rich database on breast cancer risk factors. These findings are useful for health services planning, including screening and the development of specific guidelines for the follow-up of breast cancer patients.

Key-words

Second primary tumours, Breast cancer, Aalen-Johansen estimator, Tumour size.

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Abstract

Women with a diagnosis of breast cancer are at increased risk of second primary cancers, and the identification of risk factors for the latter may have clinical implications.

We have followed-up for 11 years 10,045 women with invasive breast cancer from a European cohort, and identified 492 second primary cancers, including 140 contralateral breast cancers. Expected and observed cases and Standardized Incidence Ratios (SIR) were estimated using Aalen-Johansen Markovian methods.

Information on various risk factors was obtained from detailed questionnaires and anthropometric measurements. Cox proportional hazards regression models were used to estimate the role of risk factors.

Women with breast cancer had a 30% excess risk for second malignancies (95% confidence interval - CI - 18-42) after excluding contralateral breast cancers. Risk was particularly elevated for colorectal cancer (SIR, 1.71, 95% CI 1.43-2.00), lymphoma (SIR 1.80, 95% CI 1.31-2.40), melanoma (2.12; 1.63-2.70), endometrium (2.18; 1.75-2.70) and kidney cancers (2.40; 1.57-3.52). Risk of second malignancies was positively associated with age at first cancer, body mass index and smoking status, while it was inversely associated with education, post-menopausal status and a history of full-term pregnancy.

We describe in a large cohort of women with breast cancer a 30% excess of second primaries. Among risk factors for breast cancer, a history of full-term pregnancy was inversely associated with the risk of second primary cancer.

Introduction

Multiple primary malignancies are independent cancers (i.e. not metastases) that arise subsequently to a first malignancy, at the same site or in different parts of the body. During last decades, improvements in medical and surgical treatments have substantially increased the chances of surviving from a cancer. Cancer survivors now represent more than 3.5% of the population in the US[1], and about 3% in Western Europe[2]. Cancer survivors face the problem of subsequent primary tumours, possibly related to the late effects of treatment or to a common aetiology for multiple cancers.

Previous investigations suggested that cancer patients have a 15-20% higher risk of a second primary cancer compared with the general population. Approximately one third of cancer survivors aged >60 years are diagnosed at least once with a second cancer[3]. Women with breast cancer as first primary were the largest group of multiple cancer patients in the United States in 2002, while the second and third groups were men and women with a diagnosis of primary colorectal cancer and men with prostate cancer, respectively[4]. Descriptive data on multiple primary cancers[4-9] suggest that there is a generalised excess for several tumour types among cancer survivors.

There is a growing interest in identifying possible causes of multiple malignancies and research has focused so far on host factors, such as hormonal and/or genetic factors[10], lifestyle and environment, or treatment of the first cancer[14]. In particular, it is well established that radiotherapy can induce acute myeloid leukaemia (during the first two years after treatment[15]) and breast and thyroid cancers[16]. Acute myeloid leukemia is a late effect of adjuvant chemotherapy for breast cancer, as a consequence of prior exposure to alkylating agents and to topoisomerase II inhibitors[17]. Moreover, an increased risk of endometrial cancer was associated with a late effect of Tamoxifen therapy. Two recent papers from cancer registries in the United States[20] and in England[21] analysed the role of

radiotherapy on the risk of developing a second tumour. Both studies estimated that about 8% of second tumours are due to radiotherapy.

The aims of our study were to assess the incidence of second primary malignancies in a large prospective European cohort of breast cancer patients, and to identify risk factors for second primary cancers. We report on a population-based study of 10,045 women with newly diagnosed breast cancer, with a rich database on breast cancer risk factors that were not available in previous investigations.

Subjects and methods

The EPIC cohort

The European Prospective Investigation into Cancer and Nutrition (EPIC) study was designed as a prospective study to investigate the relationship between diet, lifestyle, genetic and environmental factors and the incidence of cancer and other chronic diseases. The study has been extensively described elsewhere. Briefly, more than 500,000 healthy subjects aged 35-70 years (~70% women) were recruited from 1992 to 1998 in 23 centres from 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom. Most of the subjects were recruited from the general population, except the French cohort (based on members of a national health insurance plan mostly covering teachers), the Utrecht and the Florence cohorts (based on women attending breast cancer screening programmes), part of the other Italian and Spanish cohorts (based on blood donors) and the Oxford cohort (based mostly on vegetarians). All participants signed an informed consent form. Approval for this study was obtained from the ethical review boards of the International Agency for Research on Cancer and of all local participating centres.

Lifestyle and dietary questionnaires

All subjects completed two questionnaires and about 80% of them donated a blood sample. A lifestyle questionnaire was used to investigate reproductive histories (including the number of pregnancies) , use of hormones (including HRT), education, physical activity, lifetime history of smoking and alcohol intake, occupation, history of major diseases (such as cancer, hypertension, diabetes) and history of surgical operations. A dietary questionnaire was used to investigate the previous year's diet and was based on 88 to 266 centre-specific food items[24].

Follow-up and identification of second cancers

The follow-up was based on population cancer registries, except in France, Germany and Greece, where a combination of methods, including health insurance records, cancer and pathology registries and active follow-up were used.

Incident cancers (eg. primary cancers occurring after the subject's recruitment in the EPIC Study) were coded using the International Classification of Diseases for Oncology, 3rd revision. Breast cancers included all cancers with invasive behaviour, "C50" as topography and all morphologies that were not from 9800 to 9949 (leukaemias) and not 959*, from 9650 to 9673, 976*, 982*, 983* and 985* (lymphomas).

After exclusion of prevalent cancer cases (all but non-melanoma skin cancer), in order to identify only women with breast cancer as their first cancer, and cases identified using death certificate only, each primary malignancy in a single patient was recorded as a separate entry. The IARC and IACR rules[25] have been used to establish whether the newly detected tumour in the same patient was a new primary tumour, an extension or a recurrence of an existing cancer. In particular, only one tumour in an organ or pair of organs or tissue was included (with the exception of systemic or multicentre cancer, potentially involving many discrete organs, and some specific histologies that are considered to be different for the purpose of defining multiple tumours; e.g. adenocarcinomas and sarcomas in the same organ are considered as two primaries). Following these rules,

contralateral breast cancer should not be registered as a second primary, unless it belongs to a different histology type. However, contralateral breast cancer was registered within some of the EPIC cohorts (France, United Kingdom, the Netherlands, Sweden, Denmark and Norway); therefore, we have estimated separately the incidence of second breast cancers in these areas. We excluded from our analysis non-melanoma skin cancers and synchronous tumours (i.e. same date of incidence).

Statistical analyses

Estimation of incidence rates and ratios

To correctly assess the incidence of second primary tumours, we applied a Markov model estimating the transition intensities from first to second tumour with the Aalen-Johansen (AJ) estimators[26], as usually done in competing risk models.[8] The model satisfies the Markov assumption, since it does not take into consideration past transitions from healthy state to first tumour. The Markov model was applied to the cohort with two different irreversible and reciprocally exclusive outcomes: death and second tumour occurrence. To estimate expected numbers, occurrence probabilities - conditioned on the occurrence of a second cancer or death - were computed in each time interval with the Aalen-Johansen method, in the framework of a Markov process.

Standardized Incidence Ratios (SIR) were used to compare expected (following general EPIC cohort rates) and observed numbers of second primary cancers[27]. Analyses of contralateral breast cancers were limited to centres that registered them.

Risk factors analysis

The differences between the women with breast cancer only and those with a second primary were tested using chi-square tests or t-tests, for qualitative and quantitative variables, respectively. Crude semi-parametric Cox proportional hazards regression models were computed to investigate the role

of baseline risk factors (age, BMI, smoking status, alcohol, hormone use, education, menopausal status, pregnancy, number of children, nutrients) in the development of a second tumour after breast cancer. In the Cox model, women started accruing person time after the diagnosis of first tumour and were censored at death or at second tumour diagnosis or at the end of follow-up. A fully adjusted model was also performed to take into account possible confounding factors. Analyses were performed for all second tumours, for all second tumours except breast cancer, and for each group of second tumours (women with a self-declared hysterectomy at the baseline were excluded from the corpus-uteri analyses). Subjects with missing values for some of the variables in the models were excluded from the analysis. An analysis by stage (PT1 – Primary Tumour stage 1 – vs PT2 and PT1 vs PT3 or more) was performed in the sub-sample for which these data are available. All analyses were performed using SAS v 9.2 (SAS Institute Inc., Cary, NC, USA) and STATA/IC 10.1 (StataCorp LD, College Station, TX, USA).

Results

A total of 368,010 women were recruited in the EPIC studies and 19,953 were excluded form this study because of a prevalent tumour. Incident rates are consistent with the general population.

Table 1 shows the general characteristics of the cohort of 10,045 women who developed breast cancer over the 11 years of follow-up in the EPIC cohort. Women with breast cancer only differed from those who developed second primary cancers with regard to smoking status, educational level, menopausal status, history of full term pregnancy and TNM status, with statistically significant differences in univariate analyses. We found no statistically significant differences concerning age (mean age in both cohorts: 60), BMI (borderline significant with an excess of overweight and obese women in the cohort with second primary malignancies), history of breast feeding, and intake of major nutrients .

Table 2 shows the age-standardized incidence rates of second primaries by country and broad European areas. Rates are overall higher in Northern Europe. Rates in Greece and Spain are unstable due to small numbers. Standardized Incidence Ratios by site of second primary cancer, and their 95% confidence intervals are shown in Table 3. Overall, there is a 30% excess of second primary cancers if we exclude breast cancers as second malignancy; if we include them, the excess is 18%, but it is estimated in a limited number of countries only. The excess was more apparent for colorectal cancer (SIR 1.71, 95% CI 1.43-2.0), melanoma (2.12; 1.63-2.70), endometrium (2.18; 1.75-2.70), lymphoma (1.80; 1.31-2.40) and kidney cancers (2.40; 1.57-3.52). When we grouped together second cancers potentially attributable to local radiotherapy for breast cancer (oesophagus, stomach, lung, thyroid), the excess was 33%, very similar to the overall excess.

When we considered the association of second primaries with risk factors for breast cancer (Table 4), risk of second primary malignancies was positively associated with age at first cancer, BMI, and smoking status, while an inverse association was found with educational level, postmenopausal status, and history of full-term pregnancy. The change of the effect of postmenopausal status from univariate to multivariate model is mainly due, as expected, to the age-adjustment. We also considered alcohol intake, use of hormone replacement therapy and the number of pregnancies, but none of these variables showed an association with risk (data not shown). Age at first tumor was a risk factor for all the sub-sites analyzed (Supplementary Table 1 to 5), while education resulted negatively associated with the risk of second colon cancer only. Full term pregnancy seemed to be inversely associated with a risk of second breast and colon cancers; no effects were shown for full term pregnancy when analyses were performed excluding breast, corpus uteri, and ovarian cancer (HR: 0.73; 0.53-1.02, p-value: 0.07). Post-menopausal status resulted to be inversely associated with a risk of second colon cancer and seemed to be a risk factor for second corpus uteri cancer. An inverse association of total dietary fiber intake was found for second breast cancer and an increased risk for smokers was found, as expected, for second lung cancer.

Women with a higher stage first breast cancer (pT3 or more) were significantly at higher risk to develop any other second cancer, except breast cancer (HR: 10.99, 95% CI 7.12-16.96 for all cancer except breast; HR: 47.03, 95% CI 16.63-133.02 for colon cancer) (Table 5).

Discussion

In the present prospective study we observed an overall 30% excess of second primary cancers after a breast cancer diagnosis. Risk of second malignancies was positively associated with age at first cancer, body mass index and smoking status, while it was inversely associated with education, post-menopausal status and a history of full-term pregnancy (even if this last association disappears after exclusion of second breast, corpus uteri, and ovarian cancer).

Data from the Surveillance Epidemiology and End Results (SEER), based on 320,000 US primary breast cancer patients diagnosed after 1973, showed an excess risk for developing a second malignancy, including contralateral breast cancer (observed-to-expected ratio of 1.18), with the excess risk concentrated in patients with earlier ages at first cancer diagnosis (<40, observed-to-expected ratio 3.33) [4]. In a study from the Netherlands on 9,900 women with primary breast cancer the standardized rate ratio for the second primaries, including contralateral breast cancer, was 2.4 (95% confidence interval 2.3-2.5)[9]. Other smaller studies found excesses for all malignancies (generally with rate ratios in the order of 1.15-1.2), or for selected malignancies[5]. In a recent paper based on Spanish data[7] the authors describe a significant overall increase in the incidence of second primary cancers in the last 30 years (p-value for trend=0.007). Our result is in line with most papers.

When considering specific cancer sites, in most cases our findings were consistent with previous observations, including for endometrium, colorectum, oesophagus, lung, thyroid and melanoma. We found a substantial increase in risk of developing a second primary kidney cancer after a breast cancer. This finding is novel, as kidney cancer was not observed to occur more frequently after a first

primary breast cancer diagnosis in any of the previously cited studies. In addition, we did not observe an excess for ovarian cancer, sarcomas, bone cancers and leukaemias unlike other investigations. Also, the excess in risk that we observed for contralateral breast cancer, in the areas where this was investigated, was lower than found elsewhere. These discrepancies could be in part attributed to variability in case completeness across centres, even if most of the areas in which our study was conducted are covered by cancer registries with a coverage that is supposed to be close to 100% according to IARC's Cancer in Five Continents programme[25]. A possible explanation could be the higher socio-economic status of the EPIC participants compared to the general population observed in population-based studies. Another alternative explanation for the higher incidence of second primary tumours observed in our study could be a more intensive screening approach in women diagnosed with breast cancer; however, this hypothesis is not supported by the apparent protective effects of a higher social class.

Several hypotheses have been put forward to explain the site-specific excesses of second primary cancers in women with a primary breast cancer. A study based on the Piedmont Cancer Registry[8] found an overall increased risk after 5 years since a diagnosis of first breast cancer, with a peak at 8 years, for cancers located in the oesophagus, stomach, lung or thyroid, suggestive of a late effect of local radiotherapy of the breast tumour. However, the conclusions of a large study in the US SEER population suggest that radiotherapy is responsible only for a small proportion of second primaries, i.e. 8% (95% CI 7-9)[20]. In the same study, it was suggested that the proportion of second primary cancers attributable to radiotherapy for breast cancer was even smaller, 5% (95% CI 4-6). Most second primary cancers seemed to be attributable to other factors, such as lifestyle and genetics. Tamoxifen has been suggested to explain the excess of endometrial cancer, and chemotherapy the excess of leukemias (that we did not evaluate due to paucity of cases)[17]. A first pancreatic cancer was associated with multiple second primary malignancies in one study[28] although breast cancer was not one of the common occurrences.

Unlike previous investigations, we had extensive information on cancer risk factors, including reproductive history, anthropometric measures, dietary and other lifestyle information such as physical activity. Some of these variables remained statistically significant after adjustment for multiple covariates: age at first cancer, smoking status, education, menopausal status, and history of full term pregnancy. Being a never smoker, high educational level and post-menopausal status were weakly associated with a reduction of risk of second primary cancers. A history of full-term pregnancy is apparently associated with an inverse risk of second primary tumours, though there was no trend with an increasing number of children (p for trend 0.169) and this association disappeared after the exclusion of second breast, corpus uteri, and ovarian cancer. The potential mechanisms for this association remain unclear. Our result is consistent with the finding from the WECARE study, in which the number of full-term pregnancies was inversely associated with contralateral breast cancer risk[29].

The analysis by sites showed expected results, due to known specific risk factors. For example women who were current smokers had an increased risk of second lung cancer; a less trivial example was the finding of a protective effect of dietary fiber for second breast cancer[30]. The main limitations of our study are the lack of information on therapies, surgical treatments after recruitment (including hysterectomy and mastectomy), and the limited information on breast cancer subtypes classified according to hormone receptor status. In spite of this, the strong excess of risk in women with more extended tumours (pT3 or more) who were probably treated with more aggressive therapies, may suggest an effect of therapies in the development of a second cancer. Moreover, the information about risk factors for the subjects involved in the EPIC study is limited to recruitment; so we cannot take into account the possible changes in risk factors, due for example to the diagnosis of the first tumour. Another limitation is that the dates of diagnosis for the cases were from 1993 onwards and therapies changed during these years (for example current radiotherapy is less toxic than radiotherapy in the early '90s). Finally, our study is limited to invasive cancers, while women with *in situ* tumours face a therapeutic approach similar to women with low-stage invasive breast cancer.

In conclusion, we describe a higher risk (30% increase) of second primary cancers in a large cohort of women with breast cancer. Several risk factors were associated with an increase (Age at first tumour, smoking status, higher stage) or a decrease (higher education, menopausal status, history of full-term pregnancy) of second primary tumours. These findings are useful for health services planning, including screening and the development of specific guidelines for the follow-up of breast cancer patients.

Conflict of Interest: none declared

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Table 1 – Descriptive analysis of baseline characteristics of the cohort of 10,045 women with breast cancer

Variable (missing values)	Person years by category	Women with breast cancer only (n=10,553)		Women with second cancers (n=492)		p-value
		Means /Number	SD/%	Means/Number	SD/%	
Age (years) (0/0)		59.81	8.48	59.96 (8.39)	8.39	0.70
BMI (0/0)						
Normal weight	32,914	6,232	59.05	264	53.66	
Overweight -	16,735	3,086	29.24	159	32.32	
Obese	6,846	1,235	11.70	69	14.02	0.05
Physical activity (925/59)						
Inactive	11,855	2,193	22.78	96	22.17	
Moderate inactive	19,414	3,582	37.20	159	36.72	
Moderate active	12,281	2,327	24.17	118	27.25	
Active	8,500	1,526	15.85	60	13.86	0.43
Smoking status (294/16)						
Never smokers	30,023	5,698	55.54	231	48.53	
Former smokers	14,059	2,591	25.26	126	26.47	
Current smokers	10,972	1,970	19.20	119	25.00	0.002
Education (288/23)						
Primary school or none	16,157	2,871	27.97	155	33.05	
Secondary school	25,854	4,882	47.56	226	48.19	
High school	12,771	2,512	24.47	88	18.76	0.006
Menopausal status (22/2)						
Premenopausal	12,464	2,523	23.96	90	18.37	
Postmenopausal	30,384	5,452	51.77	284	57.96	
Perimenopausal	11,805	2,255	21.41	95	19.39	
Bilateral ovariectomy	1,728	301	2.86	21	4.29	0.003
History of full term pregnancy (475/25)						
Never	7,290	1,380	13.69	80	17.13	
Ever	46,593	8,698	86.31	387	82.87	0.03
History of breast feeding (993/65)						
Never	7,169	1,297	15.86	54	15.56	
Ever	36,379	6,883	84.14	293	84.44	0.13
Nutrients (106/8)						
Total Fat (g/day)		77.46 (28.61)	28.61	75.28 (29.63)	29.63	0.10
Total saturated fatty acids (g/day)		30.66 (12.92)	12.92	30.30 (13.37)	13.37	0.55
Total dietary fibre (g/day)		22.18 (7.63)	7.63	21.60 (8.01)	8.01	0.10
Energy (kcal)		1,973.57 (582.91)	582.91	1,936.66 (585.46)	585.46	0.17
Stage of first Breast Cancer tumour (4479/275)						
Primary Tumour stage 1 (PT1)	21,941	4,375	72.03	125	57.60	
PT2	7,170	1,436	23.64	45	20.74	
PT3 or more	1,295	263	4.33	47	21.66	<0.001

Table 2 – Age-adjusted (WORLD population) second tumour incidence rates by country and by broad geographical region

Country	Women (N)	Person-years	Second cancers (N) °	Rate (per 1,000 per year)	Second cancers excl. breast (N)	Rate excl. breast (per 1,000 per year)
France	2865	13,061	104	7.96 (6.43-9.49)	58	4.44 (3.30-5.58)
Italy	994	5,276			35	6.63 (4.44-8.83)
Spain	463	2,602			7	2.69 (0.70-4.68)
United Kingdom	1590	8,169	82	10.04 (7.86-12.21)	71	8.69 (6.67-10.71)
The Netherlands	851	4,927	69	14.00 (10.70-17.31)	34	6.90 (4.58-9.22)
Greece	181	915			1	1.09 (0-3.23)
Germany	794	3,352	20	5.97 (3.35-8.58)	19	5.67 (3.12-8.22)
Sweden	1131	7,006	65	9.28 (7.02-11.53)	53	7.56 (5.53-9.60)
Denmark	1315	7,423	61	8.22 (6.15-10.28)	47	6.33 (4.52-8.14)
Norway	861	3,765	48	12.75 (9.14-16.35)	27	7.17 (4.66-9.88)
Southern Europe*	1638	8,793			43	4.89 (3.43-6.35)
Center Europe¶	4510	21,340	193	9.04 (7.77-10.32)	111	5.20 (4.23-6.17)
Northern Europe§	4897	26,362	256	9.71 (8.52-10.90)	198	7.51 (4.46-8.56)

* Italy, Spain, Greece; ¶ France, The Netherlands, Germany; §The UK, Sweden, Denmark, Norway

° These analyses were performed only on subjects from France, the UK, The Netherlands, Sweden, Denmark and Norway because these centres provided information on second primary breast tumours.

Table 3 – Second primary tumours after breast cancer. Standardized Incidence Ratios (SIR) and 95% Confidence Intervals (95% CI) by type of tumour (WORLD population)

Type of tumour	Observed cancer	SIR	95% CI
Colorectum	65	**1.71**	**1.43-2.04**
Pancreas	13	0.70	0.32-1.31
Lung	33	1.31	0.98-1.72
Melanoma	27	**2.12**	**1.63-2.70**
Breast*	139	**1.15**	**1.02-1.29**
Endometrium	39	**2.18**	**1.75-2.70**
Ovary	25	1.28	0.91-1.74
Kidney	16	**2.40**	**1.57-3.52**
Thyroid gland	14	**1.71**	**1.11-2.54**
Lymphomas	29	**1.80**	**1.31-2.40**
All but breast cancers	352	**1.30**	**1.18-1.42**
All cancers*	492	**1.18**	**1.06-1.31**

* These analyses were performed only on subjects from France, the UK, The Netherlands, Sweden, Denmark and Norway because these centres provided information on second primary breast tumours.

Table 4 - Analysis of risk factors for breast cancer in relation to second primary tumours: Hazard Ratios (HR) and 95% Confidence Intervals (95% CI). Multivariate model is built with all the variables in the univariate models.

Variable	**Univariate models N=492/10678**				**Multivariate model N=426/9599**			
	HR	**95% CI**		**p for trend**	**HR**	**95% CI**		**p for trend**
Age at first tumour	**1.03**	**1.02**	**1.04**	<0.001	**1.04**	**1.03**	**1.06**	<0.001
BMI								
Normal weight	Ref				Ref			
Overweight	**1.22**	**1.00**	**1.50**	0.004	1.10	0.88	1.38	0.11
Obese	**1.44**	**1.10**	**1.89**		1.29	0.96	1.74	
Smoking status								
Never smokers	Ref				Ref			
Former smokers	1.02	0.82	1.28	0.04	0.96	0.76	1.22	0.05
Current smokers	**1.30**	**1.03**	**1.64**		**1.33**	**1.04**	**1.70**	
Education								
Primary school or none (< 8 years of school)	Ref				Ref			
Secondary school (8-12 years of school)	**0.75**	**0.60**	**0.92**	<0.001	0.85	0.68	1.07	0.03
High school (> 12 years of school)	**0.63**	**0.48**	**0.82**		**0.72**	**0.53**	**0.98**	
Menopausal status*								
Premenopausal	Ref				Ref			
Postmenopausal	1.22	0.96	1.56	NA	**0.69**	**0.48**	**0.98**	NA
Perimenopausal*	1.00	0.74	1.34		0.79	0.57	1.11	
Bilateral ovariectomy	**1.75**	**1.08**	**2.83**		0.99	0.56	1.73	
History of full-term pregnancy								
Never	Ref				Ref			0.003
Ever	**0.76**	**0.60**	**0.97**	0.03	**0.68**	**0.53**	**0.87**	
Nutrients								
Total fat (g/die)	1.00	1.00	1.00	0.94	1.00	0.99	1.02	0.66
Total saturated fatty acids (g/die)	1.00	0.99	1.01	0.91	0.99	0.96	1.01	0.35
Total dietary fibre (g/die)	0.99	0.98	1.00	0.13	0.98	0.96	1.00	0.09
Energy (kcal)	1.00	1.00	1.00	0.85	1.00	1.00	1.00	0.19

* Women were considered perimenopausal if their age is in between 46 and 55 years, and the menopausal status is unknown.

Table 5 – Tumour stage as risk factor for second primary tumours among women with breast cancer: Hazard Ratios (HR) and 95% Confidence Intervals (95% CI) – Models adjusted for age at first tumour, BMI, smoking status, education, menopausal status, history of full-term pregnancy, and nutrients.

All cancer (N=217/5796)				
Primary Tumour Stage 1 (PT1) (125/4156)	Ref			<0.001
PT2 (45/1389)	1.11	0.79	1.57	
PT3 or more (47/251)	**5.38**	**3.77**	**7.67**	
All cancer but breast (N=118/5796)				
PT1 (53/4156)	Ref			<0.001
PT2 (23/1389)	1.36	0.83	2.23	
PT3 or more (42/251)	**10.99**	**7.12**	**16.96**	
Colorectum (N=29/5796)				
PT1 (5/4156)	Ref			<0.001
PT2 (9/1389)	5.15	1.71	15.55	
PT3 or more (15/251)	**47.03**	**16.63**	**133.02**	
Lung (N=7/5796)				
PT1 (1/4156)	Ref			0.002
PT2 (2/1389)	4.37	0.39	48.63	
PT3 or more (4/251)	**27.81**	**2.93**	**263.73**	
Breast (N=98/4030)*				
PT1 (72/2970)	Ref			0.86
PT2 (21/904)	0.90	0.55	1.48	
PT3 or more (5/156)	1.07	0.42	2.69	
Corpus Uteri (N=20/5796)				
PT1 (19/4156)	Ref			NA
PT2 (1/1389)	0.22	0.02	1.65	
PT3 or more (0/251)	**NA**	**NA**	**NA**	

* These analyses were performed only on subjects from France, the UK, The Netherlands, Sweden, Denmark and Norway because these centres provided information on second primary breast tumours.

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Supplementary Table 1 - Analysis of risk factors for breast cancer in relation to second COLON cancer: Hazard Ratios (HR) and 95% Confidence Intervals (95% CI)

Variable	Univariate models N=65/10678				Multivariate model N=57/9599			
	HR	95% CI		p for trend	HR	95% CI		p for trend
Age at first tumour	1,07	1,03	1,10	<0.001	1,11	1,06	1,17	<0.001
BMI								
Normal weight	Ref				Ref			
Overweight	1,34	0,77	2,33		1,01	0,56	1,83	
Obese	1,89	0,95	3,73	0,06	1,01	0,45	2,27	0,97
Smoking status								
Never smokers	Ref				Ref			
Former smokers	1,39	0,77	2,49		1,42	0,76	2,65	
Current smokers	1,21	0,62	2,35	0,45	1,38	0,68	2,80	0,29
Education								
Primary school or none	Ref				Ref			
Secondary school	0,55	0,31	0,96		0,67	0,37	1,22	
High school	0,44	0,20	0,95	0,02	0,43	0,17	1,04	0,05
Menopausal status								
Premenopausal	Ref				Ref			
Postmenopausal	1,39	0,72	2,70	0,330	0,28	0,10	0,77	0,01
Perimenopausal	0,87	0,37	2,04	0,75	0,45	0,18	1,16	0,09
Bilateral ovariectomy	1,94	0,54	6,99	0,31	0,47	0,11	2,07	0,32
Full term pregnancy								
No	Ref				Ref			
Yes	0,57	0,31	1,06	0,07	0,52	0,27	1,00	0,05
Nutrients								
Total Fat (g/die)	1,00	0,99	1,00	0,93	0,99	0,95	1,02	0,50
Total saturated fatty acids (g/die)	1,00	0,98	1,02	0,73	1,01	0,94	1,08	0,78
Total dietary fibre (g/die)	1,00	0,98	1,04	0,63	1,00	0,95	1,05	0,99
Energy (kcal)	1,00	1,00	1,00	0,48	1,00	1,00	1,00	0,25

Supplementary Table 2 - Analysis of risk factors for breast cancer in relation to second LUNG cancer: Hazard Ratios (HR) and 95% Confidence Intervals (95% CI)

Variable	Univariate models N=33/10678				Multivariate model N=26/9599			
	HR	95% CI		p for trend	HR	95% CI		p for trend
Age at first tumour	1,08	1,03	1,12	0,001	1,15	1,07	1,24	<0.001

BMI								
Normal weight	Ref				Ref			
Overweight	0,78	0,34	1,80		1,12	0,46	2,73	
Obese	1,57	0,62	3,96	0,54	1,36	0,43	4,30	0,73
Smoking status								
Never smokers	Ref				Ref			
Former smokers	2,38	0,75	7,53		2,06	0,54	7,86	
Current smokers	10,62	3,87	29,12	<0.001	9,93	3,11	31,72	<0.001
Education								
Primary school or none	Ref				Ref			
Secondary school	1,15	0,49	2,69		2,31	0,87	6,11	
High school	0,49	0,13	1,88	0,40	1,22	0,28	5,26	0,53
Menopausal status								
Premenopausal	Ref				Ref			
Postmenopausal	3,59	0,82	15,50	0,09	0,44	0,07	2,68	0,37
Perimenopausal	2,13	0,41	11,14	0,37	0,72	0,12	4,19	0,72
Bilateral ovariectomy	9,97	1,62	61,54	0,01	1,92	0,24	15,23	0,53
Full term pregnancy								
No	Ref				Ref			
Yes	0,90	0,34	2,35	0,83	0,74	0,27	2,03	0,56
Nutrients								
Total Fat (g/die)	1,00	0,99	1,01	0,97	1,03	0,98	1,08	0,29
Total saturated fatty acids (g/die)	1,00	0,97	1,03	0,95	0,92	0,83	1,02	0,10
Total dietary fibre (g/die)	0,95	0,90	1,00	0,06	0,93	0,86	1,00	0,08
Energy (kcal)	1,00	1,00	1,00	0,89	1,00	1,00	1,00	0,31

Supplementary Table 3 - Analysis of risk factors for breast cancer in relation to second BREAST cancer: Hazard Ratios (HR) and 95% Confidence Intervals (95% CI)

Variable	**Univariate models N=139/8331**				**Multivariate model N=121/7289**			
	HR	**95% CI**		**p for trend**	**HR**	**95% CI**		**p for trend**
Age at first tumour	0,98	0,96	1,01	0,22	1,02	0,98	1,06	0,28
BMI								
Normal weight	Ref				Ref			
Overweight	1,10	0,75	1,62		1,17	0,76	1,78	
Obese	1,39	0,81	2,37	0,24	1,65	0,95	2,87	0,09
Smoking status								
Never smokers	Ref				Ref			

Former smokers	1,27	0,85	1,91		1,20	0,78	1,86	
Current smokers	1,44	0,92	2,25	0,10	1,32	0,82	2,14	0,24
Education								
Primary school or none	Ref				Ref			
Secondary school	0,90	0,59	1,36		0,89	0,57	1,40	
High school	0,84	0,51	1,40	0,50	0,83	0,47	1,47	0,57
Menopausal status								
Premenopausal	Ref				Ref			
Postmenopausal	0,60	0,39	0,91	0,02	0,61	0,32	1,17	0,14
Perimenopausal	0,82	0,52	1,28	0,38	0,94	0,55	1,61	0,83
Bilateral ovariectomy	0,41	0,10	1,69	0,22	0,39	0,08	1,79	0,22
Full term pregnancy								
No	Ref				Ref			
Yes	0,64	0,41	0,99	0,04	0,58	0,37	0,90	0,02
Nutrients								
Total Fat (g/die)	1,00	0,99	1,01	0,76	1,00	0,98	1,02	0,92
Total saturated fatty acids (g/die)	1,00	0,99	1,01	0,66	0,98	0,94	1,03	0,49
Total dietary fibre (g/die)	0,97	0,95	0,99	0,02	0,95	0,91	0,99	0,007
Energy (kcal)	1,00	1,00	1,00	0,94	1,00	1,00	1,00	0,09

Supplementary Table 4 - Analysis of risk factors for breast cancer in relation to second CORPUS UTERI cancer: Hazard Ratios (HR) and 95% Confidence Intervals (95% CI)

Variable	**Univariate models N=39/10663**				**Multivariate model N=32/9587**			
	HR	**95% CI**		**p for trend**	**HR**	**95% CI**		**p for trend**
Age at first tumour	1,06	1,01	1,10	0,009	1,06	1,01	1,12	0,02
BMI								
Normal weight	Ref				Ref			
Overweight	1,59	0,78	3,24		1,59	0,72	3,51	
Obese	1,66	0,59	4,64	0,06	1,26	0,37	4,13	0,44
Smoking status								
Never smokers	Ref				Ref			
Former smokers	0,70	0,29	1,65		0,49	0,18	1,31	
Current smokers	0,68	0,24	1,89	0,36	0,57	0,18	1,80	0,20
Education								
Primary school or none	Ref				Ref			
Secondary school	0,54	0,24	1,20		0,52	0,22	1,24	

High school	0,68	0,28	1,64	0,39	0,74	0,28	2,01	0,46
Menopausal status								
Premenopausal	Ref				Ref			
Postmenopausal	2,59	1,00	6,83	0,05	1,25	0,31	5,07	0,75
Perimenopausal	1,20	0,36	3,40	0,77	0,99	0,25	3,91	0,99
Bilateral ovariectomy	NA	NA	NA	NA	NA	NA	NA	NA
Full term pregnancy								
No	Ref				Ref			
Yes	0,72	0,29	1,73	0,46	0,69	0,26	1,84	0,46
Nutrients								
Total Fat (g/die)	1,01	1,00	1,01	0,16	1,02	0,98	1,06	0,26
Total saturated fatty acids (g/die)	1,01	0,99	1,03	0,30	0,96	0,89	1,03	0,27
Total dietary fibre (g/die)	1,03	0,99	1,07	0,11	1,00	0,94	1,07	0,93
Energy (kcal)	1,00	1,00	1,00	0,14	1,00	1,00	1,00	0,84

Supplementary Table 5 - Analysis of risk factors for breast cancer in relation to ALL second cancer BUT BREAST: Hazard Ratios (HR) and 95% Confidence Intervals (95% CI)

Variable	**Univariate models N=352/10678**				**Multivariate model N=304/9599**			
	HR	**95% CI**		**p for trend**	**HR**	**95% CI**		**p for trend**
Age at first tumour	1,05	1,03	1,06	<0.001	1,05	1,03	1,07	<0.001
BMI								
Normal weight	Ref				Ref			
Overweight	1,27	1,01	1,62		1,09	0,84	1,41	
Obese	1,48	1,08	2,02	0,006	1,19	0,84	1,68	0,39
Smoking status								
Never smokers	Ref				Ref			
Former smokers	0,94	0,72	1,23		0,87	0,65	1,16	
Current smokers	1,27	0,97	1,66	0,15	1,35	1,01	1,80	0,11
Education								
Primary school or none	Ref				Ref			
Secondary school	0,69	0,54	0,89		0,85	0,65	1,11	
High school	0,56	0,40	0,77	<0.001	0,69	0,49	0,99	0,03
Menopausal status								
Premenopausal	Ref				Ref			
Postmenopausal	1,72	1,26	2,35	0,01	0,77	0,50	1,18	0,24
Perimenopausal	1,13	0,77	1,66	0,53	0,74	0,48	1,13	0,17
Bilateral ovariectomy	2,77	1,62	4,71	<0.001	1,29	0,69	2,42	0,43
Full term pregnancy								
No	Ref				Ref			

Yes	0,81	0,61	1,09	0,17	0,73	0,54	0,99	0,04
Nutrients								
Total Fat (g/die)	1,00	1,00	1,00	0,74	1,00	0,99	1,02	0,71
Total saturated fatty acids (g/die)	1,00	0,99	1,01	0,86	0,99	0,96	1,02	0,55
Total dietary fibre (g/die)	1,00	0,98	1,01	0,67	1,00	0,97	1,02	0,78
Energy (kcal)	1,00	1,00	1,00	0,81	1,00	1,00	1,00	0,63