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Family history of cancer and the risk of cancer: a network of case–control studies

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Background: The risk of many cancers is higher in subjects with a family history (FH) of cancer at a concordant site. However, few studies investigated FH of cancer at discordant sites.
Patients and methods: This study is based on a network of Italian and Swiss case–control studies on 13 cancer sites conducted between 1991 and 2009, and including more than 12 000 cases and 11 000 controls. We collected information on history of any cancer in first degree relatives, and age at diagnosis. Odds ratios (ORs) for FH were calculated by multiple logistic regression models, adjusted for major confounding factors.
Results: All sites showed an excess risk in relation to FH of cancer at the same site. Increased risks were also found for oral and pharyngeal cancer and FH of laryngeal cancer (OR = 3.3), esophageal cancer and FH of oral and pharyngeal

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cancer (OR = 4.1), breast cancer and FH of colorectal cancer (OR = 1.5) and of hemolymphopoietic cancers (OR = 1.7), ovarian cancer and FH of breast cancer (OR = 2.3), and prostate cancer and FH of bladder cancer (OR = 3.4). For most cancer sites, the association with FH was stronger when the proband was affected at age <60 years.
Conclusions: Our results point to several potential cancer syndromes that appear among close relatives and may indicate the presence of genetic factors influencing multiple cancer sites.
Key words: cancer, case–control study, epidemiology, family history, risk factors

introduction

Familial and, hence more likely, genetic factors have a relevant role in cancer risk and may interact with environmental exposures. Epidemiologists have used family history (FH), usually of first-degree relatives (FDRs), as a marker for genetic risk, knowing that FH reflects the consequences of genetic susceptibilities, shared environment, and common behaviors.

In general, subjects with a FDR affected by cancer are at higher risk than the general population for cancer of the same site [1]. However, the magnitude of the associations with FH varies between studies, cancer sites, and strata of sex and age, being generally stronger for younger probands.

In addition to well-documented familial clustering for most cancer sites, aggregation of selected types of cancers in families has also been observed. Findings of systematic analyses of the aggregation of different cancers have been published, in single reports, from the Utah [2] and Icelandic [3] population databases, the nationwide Swedish Family-Cancer Database [4] and the American Cancer Society Cancer Prevention Study-1 [5].

The first three databases [2–4] are based on unselected populations and offer important advantages in terms of lack of selection and recall bias. However, they have no information on study subjects' characteristics and lifestyle habits for adjustment purposes.

Since the early 1990s, this study group carried out a network of integrated case–control studies on cancer in Italy and Switzerland. From these data, we can compute relative risks of cancer at several sites with reference to FH of cancer at any site, adjusting for major confounding factors.

materials and methods

This investigation is part of a large network of case–control studies conducted, between 1991 and 2009, in various areas of northern (the greater Milan area; the provinces of Pordenone, Padua, Udine, Gorizia, and Forlì; the urban area of Genoa), central (the provinces of Rome and Latina), and southern (the urban area of Naples) Italy, and in the Canton of Vaud, Switzerland. Information was collected, overall, on a total of 1468 cases of cancer of the oral cavity and pharynx [6], 198 of the nasopharynx [7], 505 of the esophagus [8], 230 of the stomach [9], 2390 of the colorectum [10], 185 of the liver [11], 326 of the pancreas [12], 852 of the larynx [13], 3034 of the breast [14], 367 of the endometrium [15], 1031 of the ovary [16], 1294 of the prostate [17], 767 of the renal cell [18], and a total of 11 557 corresponding controls (supplementary Table S1, available at *Annals of Oncology* online).

All studies included incident cases, identified in the major teaching and general hospitals of the study areas. Controls were subjects admitted to the same network of hospitals of cases for a wide spectrum of acute, non-neoplastic conditions unrelated to known or potential risk factors for the corresponding cancer site. Overall, 7.5% of controls were admitted for traumatic conditions, 23.1% for nontraumatic orthopedic conditions, 32.6% for acute surgical conditions, and 36.8% for miscellaneous other illnesses.

The proportion of refusals of subjects approached was <5% in the Italian centers, and about 15% in Switzerland. The study protocols were revised and approved by the local ethics committees of the hospitals involved and all participants gave informed consent.

Cases and controls were interviewed during their hospital stay using a structured questionnaire, including information on sociodemographic characteristics, anthropometric measures, lifestyle habits (e.g. tobacco smoking and alcohol drinking), dietary habits, personal medical history, and, for women, menstrual and reproductive factors, use of oral contraceptives (OCs) and hormone replacement therapy (HRT). Subjects were specifically asked for the number of siblings, and whether they, their parents, children, grandparents or spouses were ever affected by any form of cancer (excluding nonmelanomatous skin cancer). For each relative with a history of cancer, the subject was asked to report the vital status at the time of interview, current age or the age at death, cancer site, and age at diagnosis. In our analysis, we considered the history of cancer in FDRs only, i.e. parents, siblings, and sons/daughters. On account of recall and classification difficulties, some sites were combined (i.e., all colorectum, Hodgkin and non-Hodgkin lymphoma, multiple myeloma and leukemia, as well as cervix and corpus uteri).

statistical analysis

Odds ratios (ORs) of cancer at 13 different sites according to FH of cancers in FDRs and the corresponding 95% confidence intervals (CIs) were estimated by unconditional multiple logistic regression models. The models included terms for quinquennium of age, sex (when appropriate), study center (when appropriate), year of interview, education, alcohol drinking, tobacco smoking, body mass index, and number of brothers and sisters. For female genital tract and breast cancers, models included further terms for parity, menopausal status, age at menopause, and OC and HRT use, and, for breast cancer only, age at first birth. Additional models were used to assess the potential modifying effect of sex and age at diagnosis.

To account for the effects of multiple testing, in further analyses the Benjamini–Hochberg procedure was used to control the false discovery rate at the desired level of 0.05 [19].

All statistical analyses were carried out with SAS 9.1 statistical software (SAS Institute, Cary, NC).

results

Table 1 gives the ORs and 95% CIs for 13 cancer sites according to FH of the concordant cancer, overall and by sex and age of the proband. The risk of developing cancer at a particular site increased, although not always significantly, in subjects with a FDR affected by cancer at the same site, with ORs ranging from 1.2 for nasopharyngeal cancer to 7.4 for ovarian cancer.
In general, ORs were consistent according to the sex of the proband. For most cancer sites, the association with FH was stronger when the proband was affected at age <60 years. This was more marked for liver (OR = 10.5 versus 2.1), ovarian

Table 1. Odds ratios (ORs) and 95% confidence intervals (CIs) of cancer at 13 different sites according to family history (FH) of the concordant cancer, overall and by sex and age of the proband (Italy and Switzerland, 1991–2009)

Cancer	Cases with FH (%)	Controls with FH (%)	OR[a] (95% CI)				
			Overall[b]	Sex of the proband		Age at cancer onset in the proband	
				Male	Female	<60 years	≥60 years
Oral cavity and pharynx	53 (3.6)	47 (1.2)	**2.6 (1.6–4.2)**	2.9 (1.6–5.4)	2.2 (1.0–5.1)	3.4 (1.6–7.2)	2.0 (1.1–3.9)
Nasopharynx[c]	3 (1.5)	6 (1.0)	1.2 (0.3–5.7)	1.5 (0.2–9.2)	NE[d]	NE[e]	3.4 (0.5–23.7)
Esophagus	12 (2.4)	14 (1.1)	1.7 (0.6–4.5)	1.7 (0.6–5.2)	2.2 (0.2–26.9)	0.7 (0.2–3.3)	3.1 (0.7–12.7)
Stomach	30 (13.0)	31 (5.7)	**2.7 (1.6–4.6)**	2.2 (1.0–4.8)	3.7 (1.6–8.4)	2.5 (1.0–6.2)	2.8 (1.4–5.7)
Colorectum	221 (9.2)	166 (3.4)	**2.8 (2.3–3.5)**	2.8 (2.1–3.8)	2.8 (2.0–3.9)	3.3 (2.4–4.5)	2.5 (1.9–3.3)
Liver	22 (11.9)	18 (4.5)	**3.0 (1.4–6.5)**	2.9 (1.1–7.5)	4.2 (0.9–20.5)	10.5 (1.9–59.4)	2.1 (0.9–5.1)
Pancreas	10 (3.1)	15 (2.3)	1.4 (0.5–3.3)	0.9 (0.2–3.4)	2.0 (0.5–7.8)	1.3 (0.3–5.1)	1.7 (0.5–6.1)
Larynx	29 (3.4)	27 (1.4)	**2.8 (1.5–5.1)**	3.2 (1.7–6.0)	NE[f]	3.5 (1.4–8.7)	2.2 (1.0–5.1)
Breast	311 (10.3)	145 (4.3)	**2.6 (2.1–3.2)**	–	2.6 (2.1–3.2)	2.4 (1.8–3.1)	2.8 (2.0–3.9)
Endometrium[g]	19 (5.2)	25 (3.1)	2.0 (1.0–4.0)	–	2.0 (1.0–4.0)	2.5 (0.9–6.6)	1.4 (0.5–3.6)
Ovary	27 (2.6)	9 (0.4)	**7.4 (3.3–16.6)**	–	7.4 (3.3–16.6)	20.1 (4.5–89.7)	3.2 (1.1–9.4)
Prostate	90 (7.0)	28 (1.9)	**3.9 (2.4–6.2)**	3.9 (2.4–6.2)	–	5.8 (2.3–14.6)	3.3 (1.9–5.7)
Renal cell	18 (2.3)	8 (0.5)	**4.2 (1.8–9.8)**	3.9 (1.3–11.6)	4.8 (1.2–19.9)	4.1 (1.2–13.7)	4.2 (1.2–14.4)

[a]Adjusted for age, sex (when appropriate), study center (when appropriate), year of interview, education, body mass index, alcohol drinking, tobacco smoking, and number of brothers and sisters. Reference category: no family history of the selected cancer. Odds ratios for endometrial and ovarian cancer were further adjusted for menopausal status, age at menopause, oral contraceptive and hormone replacement therapy use, and parity; odds ratios for breast cancer were further adjusted for menopausal status, age at menopause, oral contraceptive and hormone replacement therapy use, parity and age at first birth.

[b]In bold typefaced significant associations at level 0.05 after adjustment for multiple testing according to the Benjamini–Hochberg method.

[c]Nasopharyngeal cancer and family history of oral and pharyngeal cancer.

[d]Only one female case and two female controls reported a family history of oral and pharyngeal cancer.

[e]No cases of nasopharyngeal cancer with age <60 years reported a family history of oral and pharyngeal cancer.

[f]No female cases of laryngeal cancer reported a family history of laryngeal cancer.

[g]Endometrial cancer and family history of uterine cancer (including cervical and endometrial cancer, and cancer at uterus not otherwise specified).

NE, not estimable.

(OR = 20.1 versus 3.2), and prostate cancers (OR = 5.8 versus 3.3). When the proband was diagnosed before 50 years of age, the ORs for FH of the concordant cancer were even stronger, in particular for colorectal (OR = 4.3, 95% CI 2.5–7.6) and breast (OR = 3.0, 95% CI 1.9–4.5) cancers (data not shown).

Table 2 shows discordant sites with significant or borderline significant associations, overall and by sex and age of the proband. After controlling for multiple testing, the following discordant site associations were significant at $\alpha = 0.05$: oral and pharyngeal cancer and FH of laryngeal cancer (OR = 3.3), esophageal cancer and FH of oral and pharyngeal cancer (OR = 4.1), breast cancer and FH of colorectal cancer (OR = 1.5) and of hemolymphopoietic cancers (OR = 1.7), ovarian cancer and FH of breast cancer (OR = 2.3), and prostate cancer and FH of bladder cancer (OR = 3.4). For most associations, similar ORs were estimated for males and females. Some associations were somewhat stronger when cancer occurred before 60 years of age in the proband. This is particularly evident for colorectal cancer and FH of ovarian cancer (OR = 3.0 versus 1.5) and of prostate cancer (OR = 2.1 versus 1.2), endometrial cancer and FH of stomach cancer (OR = 2.8 versus 1.2), and ovarian cancer and FH of hemolymphopoietic cancers (OR = 2.0 versus 0.8). Positive (though not statistically significant) associations were found for colorectal cancer and FH of endometrial cancer (OR = 1.7, 95% CI 0.8–3.4) as well as for endometrial cancer and FH of colorectal cancer (OR = 1.6, 95% CI 0.9–2.9).

Supplementary Table S2, available at *Annals of Oncology* online shows ORs of cancer at 13 different sites for FH of the concordant cancer and FH of cancer at those discordant sites that revealed significant associations after adjustment for multiple testing by age at cancer diagnosis in the affected relative. No significant heterogeneity was found between ORs for relatives affected before and those affected after the age of 60 years, with the exception of laryngeal cancer and FH of laryngeal cancer, breast cancer and FH of breast cancer and of hemolymphopoietic cancers, endometrial cancer and FH of uterine cancer, and ovarian cancer and FH of breast cancer, for which a stronger association emerged for relatives affected at a younger age.

discussion

In this investigation, we provide a comprehensive picture of the associations between FH of cancer and cancer risk, using original data from a large network of case–control studies from Italy and Switzerland. Our data confirmed and further quantified known associations with FH of cancer at concordant sites for 13 different cancers. Several increased risks for FH of cancer at discordant sites also emerged, with the following associations remaining significant after controlling for multiple testing: oral and pharyngeal cancer and FH of laryngeal cancer, esophageal cancer and FH of oral and pharyngeal cancer, breast

Table 2. Significant or of borderline significance odds ratios (ORs) and 95% confidence intervals (CIs) of cancer at 13 different sites according to family history (FH) of discordant cancers, overall and by sex and age of the proband (Italy and Switzerland, 1991–2009)

Cancer	FH	Cases with FH (%)	Controls with FH (%)	OR[a] (95% CI)				
				Overall[b]	Sex of the proband		Age at cancer onset in the proband	
					Male	Female	<60 years	≥60 years
OP	Larynx	33 (2.2)	25 (0.7)	**3.3 (1.7–6.3)**	2.9 (1.4–6.2)	4.4 (1.4–14.0)	3.3 (1.4–7.9)	3.6 (1.4–9.3)
	Skin	8 (0.5)	7 (0.2)	3.3 (1.0–10.7)	5.1 (0.8–31.4)	2.0 (0.4–11.4)	NE[c]	5.6 (1.4–22.4)
	Breast	65 (4.4)	111 (3.0)	1.5 (1.0–2.2)	1.6 (1.0–2.5)	1.4 (0.7–2.6)	1.4 (0.8–2.4)	1.6 (0.9–2.6)
Nasopharynx	Colorectum	12 (6.1)	17 (2.9)	3.1 (1.4–7.0)	1.9 (0.7–5.1)	24.4 (3.2–189.1)	4.0 (1.5–11.0)	2.5 (0.5–12.8)
Esophagus	OP	21 (4.2)	12 (1.0)	**4.1 (1.7–9.8)**	5.6 (2.0–16.1)	NE[d]	5.0 (1.2–20.5)	3.6 (1.2–11.0)
	Stomach	29 (5.7)	39 (3.1)	1.8 (1.0–3.3)	1.6 (0.8–3.3)	2.9 (0.7–11.9)	2.5 (0.8–7.1)	1.6 (0.7–3.6)
Colorectum	Stomach	132 (5.5)	224 (4.5)	1.2 (1.0–1.6)	1.2 (0.9–1.7)	1.1 (0.8–1.6)	1.3 (0.9–1.8)	1.2 (0.9–1.6)
	Liver	91 (3.8)	141 (2.9)	1.4 (1.0–1.8)	1.1 (0.8–1.7)	1.8 (1.2–2.7)	1.5 (0.9–2.4)	1.3 (0.9–1.9)
	Ovary	15 (0.6)	17 (0.3)	2.1 (1.0–4.2)	2.6 (0.7–9.8)	2.0 (0.8–5.1)	3.0 (1.1–8.5)	1.5 (0.6–4.0)
	Prostate	39 (1.6)	55 (1.1)	1.6 (1.0–2.4)	1.5 (0.8–2.7)	1.4 (0.7–2.6)	2.1 (1.2–3.8)	1.2 (0.6–2.1)
	HLPC	52 (2.2)	82 (1.7)	1.4 (1.0–2.0)	1.4 (0.9–2.3)	1.4 (0.8–2.4)	1.3 (0.7–2.2)	1.4 (0.9–2.3)
Pancreas	Stomach	21 (6.4)	20 (3.1)	2.4 (1.2–4.7)	3.6 (1.2–10.3)	1.9 (0.7–5.0)	3.0 (0.7–11.9)	2.0 (0.9–4.5)
Larynx	Colorectum	49 (5.8)	80 (4.1)	1.5 (1.0–2.3)	1.4 (0.9–2.3)	3.5 (0.7–17.4)	1.3 (0.6–3.0)	1.6 (0.9–2.7)
	Skin	7 (0.8)	3 (0.2)	8.4 (1.7–41.8)	14.4 (1.7–125.0)	NE[e]	6.1 (1.1–33.8)	NE[f]
Breast	Stomach	148 (4.9)	138 (4.1)	1.2 (1.0–1.6)	–	1.2 (1.0–1.6)	1.3 (0.9–1.8)	1.2 (0.8–1.7)
	Colorectum	150 (4.9)	112 (3.3)	**1.5 (1.1–1.9)**	–	1.5 (1.1–1.9)	1.8 (1.3–2.6)	1.2 (0.8–1.7)
	Skin	26 (0.9)	10 (0.3)	3.0 (1.4–6.4)	–	3.0 (1.4–6.4)	1.9 (0.8–4.5)	6.2 (1.3–28.8)
	Uterus	108 (3.6)	84 (2.5)	1.4 (1.0–1.9)	–	1.4 (1.0–1.9)	1.5 (1.0–2.2)	1.2 (0.8–2.0)
	Prostate	59 (1.9)	42 (1.2)	1.6 (1.1–2.4)	–	1.6 (1.1–2.4)	1.3 (0.8–2.2)	2.1 (1.1–4.3)
	HLPC	92 (3.0)	57 (1.7)	**1.7 (1.2–2.4)**	–	1.7 (1.2–2.4)	2.0 (1.2–3.1)	1.4 (0.9–2.4)
Endometrium	Stomach	22 (6.0)	32 (4.0)	1.8 (1.0–3.4)	–	1.8 (1.0–3.4)	2.8 (1.1–7.2)	1.2 (0.5–2.7)
	Kidney	6 (1.6)	5 (0.6)	4.2 (1.0–16.5)	–	4.2 (1.0–16.5)	1.7 (0.3–11.0)	7.3 (1.1–50.3)
	Brain	10 (2.7)	7 (0.9)	4.2 (1.3–13.3)	–	4.2 (1.3–13.3)	3.5 (0.5–22.9)	3.4 (0.8–14.9)
Ovary	Colorectum	60 (5.8)	89 (3.7)	1.6 (1.1–2.4)	–	1.6 (1.1–2.4)	1.7 (1.1–2.7)	1.6 (0.8–2.9)
	Larynx	24 (2.3)	42 (1.7)	1.8 (1.0–3.2)	–	1.8 (1.0–3.2)	1.7 (0.9–3.4)	1.9 (0.6–5.7)
	Breast	104 (10.1)	111 (4.6)	**2.3 (1.7–3.2)**	–	2.3 (1.7–3.2)	1.9 (1.3–2.9)	2.8 (1.8–4.4)
	HLPC	32 (3.1)	54 (2.2)	1.6 (1.0–2.5)	–	1.6 (1.0–2.5)	2.0 (1.1–3.5)	0.8 (0.3–2.0)
Prostate	Colorectum	84 (6.5)	58 (4.0)	1.5 (1.0–2.2)	1.5 (1.0–2.2)	–	1.3 (0.6–2.8)	1.6 (1.0–2.5)
	Lung	111 (8.6)	88 (6.1)	1.5 (1.1–2.0)	1.5 (1.1–2.0)	–	1.4 (0.7–2.7)	1.5 (1.0–2.2)
	Ovary	10 (0.8)	2 (0.1)	7.4 (1.4–38.2)	7.4 (1.4–38.2)	–	0.9 (0.1–17.2)	NE[g]
	Bladder	31 (2.4)	10 (0.7)	**3.4 (1.6–7.3)**	3.4 (1.6–7.3)	–	4.0 (1.1–15.4)	3.2 (1.3–8.2)
	Kidney	16 (1.2)	6 (0.4)	3.4 (1.2–9.4)	3.4 (1.2–9.4)	–	2.7 (0.5–14.3)	3.9 (1.0–14.9)
Renal cell	Uterus	26 (3.4)	32 (2.1)	1.7 (1.0–3.0)	2.3 (1.1–4.7)	1.2 (0.5–2.8)	0.9 (0.3–3.3)	1.6 (0.9–3.0)

[a]Adjusted for age, sex (when appropriate), study center (when appropriate), year of interview, education, body mass index, alcohol drinking, tobacco smoking, and number of brothers and sisters. Reference category: no family history of the selected discordant cancer. Odds ratios for endometrial and ovarian cancers were further adjusted for menopausal status, age at menopause, oral contraceptive and hormone replacement therapy use, and parity; odds ratios for breast cancer were further adjusted for menopausal status, age at menopause, oral contraceptive and hormone replacement therapy use, parity and age at first birth.
[b]In bold typefaced, in the overall analysis, significant associations at level 0.05 after adjustment for multiple testing according to the Benjamini–Hochberg method.
[c]Only one case and three controls with age <60 years reported a family history of skin cancer.
[d]Only one female case and five female controls reported a family history of oral and pharyngeal cancer.
[e]No female case reported a family history of skin cancer.
[f]Only two cases and no control with age ≥60 years reported a family history of skin cancer.
[g]Nine cases and no control with age ≥60 years reported a family history of ovarian cancer.
HLPC, hemolymphopoietic cancers; NE, not estimable; OP, oral cavity and pharynx.

cancer and FH of colorectal cancer and of hemolymphopoietic cancers, ovarian cancer and FH of breast cancer, and prostate cancer and FH of bladder cancer.

Most of the increased risks found for FH are supported by existing evidence pointing to genetic aspects of cancer. Mutation in *BRCA1* and *BRCA2* genes are associated to breast and ovarian cancer, and (though less strongly) to other sites like colon, prostate, and pancreas [20, 21]. For discordant sites, *BRCA1/2* mutations presumably contributed to the observed clustering of breast, ovarian, colorectal and prostate cancers (an increased, although nonsignificantly, breast cancer risk was observed for FH of ovarian cancer, with an OR of 1.7).

Mutations in mismatch repair genes involved in the Lynch syndrome (i.e., *MSH2* and *MLH1*) increase the risk of colorectal and endometrial adenocarcinomas, and, to a smaller extent, ovarian cancer [22]. These mutations could therefore be responsible for part of the identified associations between colorectal and endometrial cancers and FH of cancer at concordant sites, as well as of the cluster of colorectal and ovarian cancers. We found a significant association between breast cancer and FH of hemolymphopoietic cancers, with an OR of 1.5 (95% CI 1.0–2.7) for FH of leukemia. Breast cancer and leukemia have been linked within families that have rare germline mutations in either the *p53* gene (Li-Fraumeni Syndrome) or ataxia telangiectasia gene [23].

Although most of these cancer susceptibility genes confer a high risk of developing the disease and are highly penetrant, they are too rare to account for a substantial proportion of common cancers; there may also be predisposing genes of lower penetrance that account for a larger proportion of cancers [1]. This is the case of common polymorphisms in genes involved in the metabolism of exogenous or endogenous mutagens or in the production of sex hormones or their analogues [24].

Further, environmental exposures and habits shared by family members may account for some of the observed familial clustering of cancers. In particular, alcohol and tobacco, alone or in combination, are associated with an increased risk of various cancers [25], with increased relative risks up to 100-fold for oral and pharyngeal cancer in the highest consumption level [26]. Moreover, shared dietary factors may play a role in some of the observed associations, in particular among digestive tract cancers. *H. pylori* infection, which tends to aggregate among family members [27], may contribute to the associations between FH of stomach cancer and the risk of stomach cancer and pancreatic cancer, whose risk is increased among *H. pylori*-infected subjects [28]. Another possible shared factor explaining the associations between kidney and uterine/endometrial cancers, in both directions, and breast cancer and FH of colorectal cancer is obesity, which increases the risk of these cancers [29] and runs in families. For the breast–FH of prostate cancer association, potentially shared hormonal mechanisms have recently been suggested [30].

Some of the discordant site associations that emerged in our analyses, such as those between oral and pharyngeal cancer and FH of skin cancer, or nasopharyngeal cancer and FH of colorectal cancer, have not been consistently reported in the literature and may be chance findings; any inference remains therefore speculative. Some others are based on a limited number of exposed cases and controls and need independent confirmation. On the other hand, we cannot exclude that some existing associations did not emerge in our analysis due to insufficient statistical power, particularly when the strength of the relation is modest, or the cancer(s) is rare.

Some of our findings on cross site associations have been previously reported from studies conducted on population-based databases [2–4]. These include clusters of prostate, kidney and bladder cancers [2–4], prostate and colorectal cancers [2, 3], ovarian and breast cancers [3, 4], breast and prostate cancers [3, 4], and colorectal and prostate cancers [2, 3]. Moreover, consistently with our findings, the Swedish database showed an association between colorectal and breast cancers [4].

In our case–control studies, selection bias should be limited as we included in the control group subjects admitted to hospital for a wide spectrum of acute, non-neoplastic conditions, unrelated to the major risk factors for cancer. Moreover, the almost complete participation has likely reduced selection bias. The male/female ratio was high for several cancer sites, and particularly for oral cavity and pharynx, nasopharynx, esophagus, liver, and larynx. This reflects actual differences observed in Italy in the incidence of these cancers between the two sexes. This is not surprising in our population, where (combined) alcohol and tobacco consumption was considerably more common in men than women in the past.

Data on FH of cancer was self-reported, and it is possible that cancer patients may be more interested in understanding their family cancer history in greater detail, especially if multiple family members have been affected by a specific cancer. However, the similar hospital setting of the interview should have improved the comparability of the information collected. An analysis in our population showed a satisfactory reliability of data on FH of all cancers provided by hospital controls, with a kappa statistic of 0.70 for all cancers, 0.70 for liver cancer, and 0.80 for any digestive tract cancers [31]. In a recent systematic review from the US Agency for Healthcare Research and Quality, self-reported FH of common cancers appeared to be fairly accurate: specificity across all cancer types ranged from 91% to 99%, while sensitivity values showed greater variability, with breast cancer having the highest values (around 85%–90%) [32]. In the Connecticut Family Health Study, reports from FDRs were more accurate than those from second degree relatives; we therefore considered FDRs only in our analysis [33]. With reference to confounding, we were able to adjust for the main recognized risk factors, including tobacco smoking, alcohol drinking, overweight/obesity, and, for female genital tract and breast cancers, reproductive factors.

In the analysis of the association between 13 different cancer sites and FH of cancer at 18 sites, the total number of available comparisons is 234, and the problem of multiple comparisons is an important issue. Several adjustment techniques have been proposed recently [19], and we checked for consistency of results obtained according to traditional and newly developed methods. However, in conformity with the exploratory aim of this study and with the existing literature, we commented both adjusted and unadjusted results for multiple comparisons, though more relevance should be given to associations that were still significant after adjustment for multiple testing.

In conclusion, our results point to several potential cancer syndromes that appear among close relatives and may indicate the presence of genetic factors influencing multiple cancer sites.

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disclosure

The authors have declared no conflicts of interest.

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