Are Twins at Risk of Cancer: Results From the Swedish Family-Cancer Database

Kari Hemminki[1,2] and Bowang Chen[1]

[1] *Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany*
[2] *Department of Biosciences at Novum, Karolinska Institute, Sweden*

A few twin studies on cancer have addressed questions on the possible carcinogenic or protective effects of twining by comparing the occurrence of cancer in twins and singletons. The nationwide Swedish Family-Cancer Database of 10.2 million individuals and 69,654 0- to 70-year-old twin pairs were used to calculate standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for all main cancers compared to singletons. The overall risk of cancer in same- or different-sex twins was at the same level as the risk for singletons. Testicular cancer, particularly seminoma, was increased among same-sex twins (1.54) and all twins to an SIR of 1.38. Among other tumors, neurinomas and non-thyroid endocrine gland tumors were increased. Colorectal cancers and leukemia were decreased among all twins. Melanoma and squamous cell skin cancer were decreased in male same-sex twins. The data on this unselected population of twins suggest that twinning per se is not a risk factor of cancer. *In utero* hormonal exposures or postnatal growth stimulation may be related to the risk of testicular cancer and pituitary tumors. Protective effects against colorectal cancer may be related to a beneficial diet, and in melanoma and skin cancer, to socioeconomic factors. The study involved multiple comparisons, and internal consistency between the results was one of the main factors considered for their plausibility. The results should encourage others working on twin and singleton populations to examine the specific associations and emerging hypotheses.

Twin data have been used in the estimation of cancer heritability by calculating risks for twins of affected probands, that is, probandwise comparisons (Ahlbom et al., 1997; Lichtenstein et al., 2000). In another group of studies, twins have been compared to singletons and the risks have been calculated for all twins irrespective of the proband status (Hemminki & Li, 2002; Iversen et al., 2001). The rationale for the latter type of study is that twins differ from singletons in birthweight, gestational age and in intrauterine environment. Maternal serum estrogen levels are higher in twin pregnancies compared to singletons, and this has been the theme of a number of studies, particularly on breast cancer testing the maternal estrogen hypothesis (Cerhan et al., 2000; Ekbom et al., 1997; Hsieh et al., 1992; Hubinette, Cnattingius, et al., 2001; Hubinette, Cnattingius, et al., 2001; Kaijser et al., 2001; Ros et al., 2001; Swerdlow et al., 1997; Trichopoulos, 1990; Verkasalo et al., 1999). However the comparisons of breast cancer risks between twins and singletons have remained inconclusive (Cerhan et al., 2000; Ekbom et al., 1997; Iversen et al., 2001; Swerdlow et al., 1996; Verkasalo et al., 1999). In contrast to breast cancer, a limited number of other cancers have been used in comparing risks between twins and singletons (Milan et al., 1998; Swerdlow et al., 1996). In yet another type of study, characteristics of twins concordant and discordant for cancer have been compared (Hamilton & Mack, 2003; Mack et al., 2002; Swerdlow et al., 2002; Swerdlow et al., 1999).

The ad hoc twin datasets and registers have been collected by initially identifying living twins who have been contacted through a call or a questionnaire involving some form of selection (Cerhan et al., 2000; Hamilton & Mack, 2003; Iversen et al., 2001; Lichtenstein et al., 2000). However, twin births can be identified from population databases that may cover the whole population and require no conditions for the twins to be included. The nationwide Swedish Family-Cancer Database, in which the birth dates of the whole population are recorded, has previously been used to study cancer risks in twins (Hemminki & Li, 2002). The database has been updated twice since that study and in the current version, 139,308 twins have been identified and over 3000 of these diagnosed with cancer, which is 60% more than in the previous study. The increase in the number of cases particularly affected cancers diagnosed at an advanced age, such as prostate cancers, for which the numbers of cancers trebled since the previous study. As another novel feature, we examine specific anatomic sites and histologies. We report here cancer risks in twins compared to singletons with 170,000 diagnosed cancers.

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Address for correspondence: Kari Hemminki, Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580, 69120 Heidelberg, Germany. E-mail: k.hemminki@dkfz.de

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Subjects and Methods

Statistics Sweden maintains a 'Multigeneration Register', where individuals born in 1932 and later in Sweden are registered with their parents (those registered as parents at birth) and organized as families (Hemminki et al., 2001). Information on the database is also available at the Nature Genetics web site as 'Supplementary information' (Hemminki & Granström, 2002). The data on families and cancers have complete coverage, barring some groups of deceased offspring born in the 1930s and who died before 1991. Although this small group of offspring with missing links to parents has a negligible effect on risk estimates (Hemminki & Li, 2003), the present study was limited to offspring whose parents were known, to eliminate possibility of bias. This Multigeneration Register was linked by the individually unique national registration number to the Cancer Registry for the years 1958 to 2002. Cancer registration has been considered to be close to 100% for the past 15 years at least, when most cancers in the present twin population were diagnosed (Center for Epidemiology, 2004). Twins were defined as children born to the same mother at the same time. Triplets and quadruplets were removed from the analysis.

The site of cancer was registered based on a 4-digit diagnostic code according to the 7th revision of the International Classification of Diseases (ICD-7; World Health Organization, 1955). The following ICD-7 codes were pooled: upper aerodigestive tract cancer codes 161 (larynx) and 140 to 148 (lip, mouth, pharynx), except for code 142 (salivary glands), lymphoma codes 200, 202 (non-Hodgkin's lymphoma), 201 (Hodgkin's disease) and leukemia codes 204 to 207 (leukemias), 208 (polycytemia vera) and 209 (myelofibrosis). Rectal cancer, ICD-7 code 154, was subdivided into anus (squamous cell carcinoma, 154.1) and mucosal rectum (154.0). Basal cell carcinoma of the skin is not registered in the Cancer Registry. The 4-digit code was used to separate specific subsites for nervous system and nonthyroid endocrine gland tumors. Pathology codes were used to separate testicular seminoma and teratoma.

Standardized incidence ratios (SIRs) were used to measure cancer risks for twins and the reference rate was calculated for singletons. SIR was the ratio of the observed (O) to expected (E) number of cases. The expected numbers were calculated from 5-year-age-, sex-, period- (10-year bands), area- (county), and socioeconomic status–standardized rates. Confidence intervals (CIs; 95% CI or 99% CI) were calculated assuming a Poisson distribution (Esteve et al., 1994). Follow-up was started for each individual at birth or at immigration after January 1, 1958, whichever was the latest. Follow-up was terminated on diagnosis of first cancer, death, emigration or the closing date of the study, December 31, 2002. Tabulations are shown for cancer sites with at least 20 twin patients.

Results

The Family-Cancer Database covered the years 1958 to 2002 from the Swedish Cancer Registry and included 3206 cancers from 69,654 identified twin pairs aged 0 to 70 years. Of the affected twins, 1935 were of the same sex and 1196 were different-sexed. For calculation of SIRs for twins as compared to singletons, the data were adjusted for sex, age, period, residential area and socioeconomic status. The SIR of all cancers was 0.98, and for male twins of the same sex, the SIR decreased to 0.93, which was of borderline significance (Table 1). For all twins, SIRs were increased for testicular cancer (SIR 1.38) and nonthyroid endocrine gland tumors (1.26); SIRs were decreased for colon (0.82) and colorectal (0.81) cancers and for leukemia (0.81). Among male twins, testicular cancer was increased to a SIR of 1.46. Among same-sexed twins, melanoma and squamous cell skin cancer was decreased for men (0.75 and 0.56, respectively); among different-sexed twins, gastric cancer was increased for men (1.94) and lung cancer for women (1.58). As multiple comparisons are of concern in these analyses, 99% CIs for the significant SIRs are underlined in the table. Only the SIRs for colorectal and testicular cancers and female colon and lung cancers remained significant at the 1% level.

For certain cancer sites of interest, analysis was carried out by histological or anatomic location (Table 2). The increase in testicular cancers among same-sex twins was due to seminomas more than to teratomas. The only nervous system tumor showing an excess was neurinoma, with an SIR of 1.53 for all twins. Parathyroid tumors were in excess among all twins (1.33) and pituitary tumors among same-sex women (1.90). The acute and chronic subtypes of lymphatic and myeloid leukemias were also analyzed separately but none of these showed a significant decrease, which was observed for all leukemia (data not shown); the SIR for acute lymphatic leukemia, the most common childhood leukemia accounting for 52 of the 123 leukemia cases, was 1.00.

Discussion

Multiple comparisons are a problem in these kinds of studies, and despite there being a number of formal statistical ways to deal with the issue, none of them are universally accepted (Rothman & Greenland, 1998; Wacholder et al., 2004). Many independent comparisons were done (Table 1), and undoubtedly some of the observed changes were fortuitous. Higher significance levels may be required in exploratory types of studies (99% CIs are specified here). Other means of judging the plausibility of the results are to evaluate them in terms of biological rationale, previous findings and consistency between same- and different-sexed twins and between male and female twins. Although the responses may differ between genders and monozygotic (MZ) and dizygotic (DZ) twins, the first assumption is that an effect should be

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Table 1

Risk of Cancer in Twins

Cancer site	Same-sex twins								Different-sex twins								All			
	Male				Female				Male				Female							
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Upper aerodigestive tract	28	1.00	0.67	1.45	14	1.09	0.60	1.84	20	1.18	0.72	1.83	9	1.23	0.56	2.35	71	1.09	0.85	1.38
Stomach	8	0.51	0.22	1.00	14	1.28	0.70	2.15	19	**1.94**	1.17	3.04	6	0.94	0.34	2.05	47	1.09	0.80	1.46
Colon	42	1.01	0.73	1.37	29	**0.60**	0.40	0.86	21	0.83	0.51	1.27	26	0.93	0.61	1.36	118	**0.82**	0.68	0.99
(right-sided)	14	0.84	0.46	1.41	11	0.59	0.29	1.06	12	1.17	0.60	2.05	6	0.55	0.20	1.21	43	0.76	0.55	1.03
(left-sided)	17	1.18	0.68	1.89	9	0.59	0.27	1.12	7	0.78	0.31	1.61	11	1.23	0.61	2.22	44	0.92	0.67	1.24
Rectum	23	0.82	0.52	1.23	16	0.72	0.41	1.17	16	0.91	0.52	1.48	9	0.69	0.31	1.32	64	0.79	0.61	1.01
Colorectum	65	0.93	0.72	1.19	45	**0.63**	0.46	0.85	37	0.86	0.61	1.19	35	0.85	0.59	1.19	182	**0.81**	0.70	0.94
Liver	13	1.06	0.56	1.82	9	0.71	0.32	1.35	8	1.10	0.47	2.19	10	1.38	0.66	2.55	40	1.01	0.72	1.38
Pancreas	13	1.01	0.54	1.73	15	1.24	0.69	2.06	3	0.38	0.07	1.12	7	0.99	0.39	2.06	38	0.95	0.67	1.31
Lung	40	0.85	0.61	1.16	46	1.01	0.74	1.35	26	0.90	0.59	1.32	42	**1.58**	1.14	2.13	154	1.04	0.88	1.22
Breast	0				422	1.00	0.90	1.10	1	1.48	0.00	8.49	263	1.07	0.95	1.21	686	1.02	0.95	1.10
Cervix	0				66	0.93	0.72	1.18	0				45	1.10	0.80	1.47	111	0.99	0.82	1.19
Endometrium	0				56	1.00	0.76	1.30	0				41	1.26	0.90	1.70	97	1.09	0.89	1.34
Ovary	0				62	0.91	0.70	1.17	0				44	1.12	0.81	1.51	106	0.99	0.81	1.19
Prostate	95	0.87	0.70	1.07	0				80	1.14	0.91	1.42	0				175	0.98	0.84	1.13
Testis	77	**1.46**	1.15	1.83	0				35	1.22	0.85	1.70	0				112	**1.38**	1.13	1.66
Kidney	26	0.90	0.59	1.32	16	0.79	0.45	1.28	18	1.06	0.62	1.67	8	0.71	0.30	1.40	68	0.88	0.68	1.11
Urinary bladder	35	0.81	0.57	1.13	19	1.22	0.73	1.91	25	0.94	0.61	1.39	12	1.33	0.68	2.33	91	0.97	0.78	1.19
Melanoma	49	**0.75**	0.55	0.99	85	0.97	0.77	1.20	34	0.88	0.61	1.23	45	0.90	0.66	1.21	213	0.88	0.77	1.01
Skin	12	**0.56**	0.29	0.98	19	1.20	0.72	1.87	13	1.01	0.53	1.72	8	0.87	0.37	1.72	52	0.88	0.65	1.15
Nervous system	92	1.15	0.92	1.41	96	1.18	0.96	1.44	38	0.90	0.64	1.24	42	0.97	0.70	1.31	268	1.09	0.96	1.22
Thyroid gland	9	0.95	0.43	1.82	27	0.91	0.60	1.33	7	1.27	0.50	2.64	11	0.65	0.32	1.18	54	0.88	0.66	1.15
Endocrine glands (other)	29	1.28	0.85	1.83	51	**1.38**	1.03	1.82	16	1.22	0.69	1.98	22	1.04	0.65	1.58	118	**1.26**	1.04	1.51
Bone	10	0.90	0.43	1.66	5	0.68	0.22	1.60	9	1.70	0.77	3.24	4	1.11	0.29	2.88	28	1.03	0.68	1.48
Connective tissue	6	0.46	0.17	1.01	11	0.88	0.44	1.58	6	0.86	0.31	1.88	7	1.05	0.42	2.17	30	0.77	0.52	1.09
NHL	48	0.98	0.73	1.31	21	0.68	0.42	1.05	30	1.09	0.74	1.56	14	0.82	0.45	1.38	113	0.91	0.75	1.10
Hodgkin's disease	20	1.00	0.61	1.55	12	0.81	0.41	1.41	5	0.47	0.15	1.11	7	0.90	0.36	1.87	44	0.83	0.60	1.11
Myeloma	9	0.99	0.45	1.89	8	1.21	0.52	2.39	3	0.53	0.10	1.58	3	0.78	0.15	2.30	23	0.91	0.58	1.37
Leukemia	44	0.76	0.55	1.03	35	0.79	0.55	1.10	22	0.78	0.49	1.19	22	1.01	0.63	1.53	123	**0.81**	0.67	0.97
All	751	**0.93**	0.86	1.00	1184	0.97	0.92	1.03	471	1.00	0.91	1.10	725	1.05	0.97	1.13	3131	0.98	0.95	1.02

Note: Bold type = 95% CI does not include 1.00; underlined type = 99% CI does not include 1.00.

NHL = Non-Hodgkin's lymphoma.

Table 2
SIR for Cancer in Twins at Specific Sites

Cancer site	Same-sex twins								Different-sex twins							
	Male				Female				Male				Female			
	0	SIR	95% CI		0	SIR	95% CI		0	SIR	95% CI		0	SIR	95% CI	
Testis	77	**1.46**	1.15	1.83	0				35	1.22	0.85	1.70	0			
Teratoma	33	1.29	0.89	1.81	0				18	1.35	0.80	2.14	0			
Seminoma	40	**1.54**	1.10	2.09	0				17	1.15	0.67	1.84	0			
Nervous system	92	1.15	0.92	1.41	96	1.18	0.96	1.44	38	0.90	0.64	1.24	42	0.97	0.70	1.31
Neurinoma	17	1.71	0.99	2.74	12	1.36	0.70	2.38	8	1.40	0.60	2.76	8	1.62	0.69	3.21
Meningioma	11	1.38	0.68	2.47	23	1.05	0.66	1.58	4	0.84	0.22	2.18	14	1.10	0.60	1.85
Glioma	40	1.07	0.76	1.46	34	1.13	0.79	1.59	18	0.91	0.54	1.44	15	0.96	0.53	1.58
Ependymoma	4	0.87	0.23	2.24	3	0.88	0.17	2.60	3	1.34	0.25	3.97	1	0.59	0.00	3.37
Non-thyroid endocrine	29	1.28	0.85	1.83	51	**1.38**	1.03	1.82	16	1.22	0.69	1.98	22	1.04	0.65	1.58
Adrenal	4	1.02	0.27	2.65	7	1.39	0.55	2.89	2	0.98	0.09	3.61	1	0.36	0.00	2.08
Parathyroid	9	1.11	0.50	2.12	26	1.22	0.80	1.79	7	1.45	0.57	3.00	20	1.62	0.99	2.50
Thymic	2	1.87	0.18	6.87	2	1.62	0.15	5.96	3	4.94	0.93	14.64	0			
Pituitary	13	1.55	0.82	2.66	15	**1.90**	1.06	3.14	4	0.81	0.21	2.09	1	0.22	0.00	1.28

Cancer site	All			
	0	SIR	95% CI	
Testis	112	**1.38**	1.13	1.66
Teratoma	51	1.31	0.98	1.72
Seminoma	57	**1.39**	1.06	1.81
Nervous system	268	1.09	0.96	1.22
Neurinoma	45	**1.53**	1.11	2.05
Meningioma	52	1.10	0.82	1.44
Glioma	107	1.04	0.85	1.26
Ependymoma	11	0.92	0.46	1.65
Non-thyroid endocrine	118	**1.26**	1.04	1.51
Adrenal	14	1.02	0.56	1.72
Parathyroid	62	**1.33**	1.02	1.70
Thymic	7	1.94	0.77	4.01
Pituitary	33	1.28	0.88	1.80

Note: Bold type = 95% CI does not include 1.00; underlined type = 99% CI does not include 1.00.

reproduced in several twin groups. For example, if low birthweight is affecting cancer risks, the results should be consistent between same- and different-sexed twins and between the genders (a total of four comparisons, two for gender-specific cancers). As the increased risks for gastric and lung cancers were observed for one gender in a single twin type (in one of four comparisons), the results may be fortuitous and are not discussed further. In discussing other findings, internal consistencies in addition to the formal statistical significance are emphasized.

The birthweight of Swedish twins was 2575g in 2001, which was 72% of the birthweight of singletons (3574g; The Swedish Maternity Registry at the Swedish National Board of Health and Welfare, http://www.sos.se). However, singletons weighed only 69% of the combined weight of twins. Thus twinning may alter cancer risks for many reasons, such as low birthweight, the fast catch-up postnatal growth period, space limitations and maternal hormonal and metabolic responses to the twin pregnancy. In the present study on an unselected population of twins, the SIRs for all cancer were at the level exactly of the singleton population (SIR 0.98), indicating that twinning per se is no risk factor for cancer. This is reassuring for studies on heritability as the reference rates in twins are at the level of singletons. In previous large twin studies, the overall cancer incidence rates have been somewhat below those of singletons (Iversen et al., 2001; Verkasalo et al., 1999).

At specific histologies and tumor sites, increased risks were noted for testicular cancers, neurinomas and pituitary tumors. None of these results could be reproduced in same- and different-sexed twins but neurinomas were nonsignificantly increased in all four comparisons. The postnatal catch-up phase of weight gain is stimulated by the pituitary growth hormone, and the excess of pituitary tumors could be related to the small birthweight. However, no effect was observed for different-sex twins. Moreover, if true, these tumors should be in excess in singletons with a low birthweight, but no literature was found on the issue. A rare hormonal disorder, acromegaly, is characterized by the presence of pituitary adenomas that overproduce growth hormone; however, no reports on the occurrence of neurinomas or testicular cancers in acromegaly patients are available (Colao et al., 2004). Increases for testicular cancer were found particularly for seminomas in same-sex twins, and to a lesser extent in different-sex twins. A study in the United Kingdom has reported an increase in testicular cancer in DZ twins as compared to MZ twins (Iversen et al., 2001; Swerdlow et al., 1997). In our study, the risks were higher in same-sex twins, who may experience lower *in utero* estrogen exposures than different-sex twins (Kaijser et al., 2000). Thus, the data lend limited support to the assumed testicular cancer risk posed by *in utero* exposure to estrogens or other pregnancy hormones (Moller & Skakkebaek, 1997; Weir et al., 2000; Westergaard et al., 1998).

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Apparent protection was found for colon and colorectal cancers and leukemia, and, in same-sex twins, for melanoma and squamous cell skin cancer. For leukemia, the apparent protection did not cover acute lymphatic leukemia because the SIR for this type was 1.00. The decreased risk for colorectal cancer was observed at a 99% level and it could be related to beneficial dietary factors. Decreases for melanoma and male colon cancer were also noted in the Norwegian study (Iversen et al., 2001). Although some biological mechanism cannot be excluded for the protection against melanoma and skin cancer, we suggest that it depends on socioeconomic factors. Twin birth limits the family's possibilities for sun holidays in southern countries, and thus would reduce spells for short-term excessive sun exposure for twins. Our data were adjusted for socioeconomic factors but it could not consider constrains imposed by twin pregnancies. We have shown elsewhere that children born to large families are protected against melanoma, probably also for socioeconomic reasons (Hemminki & Mutanen, 2001).

In summary, the present data on medically verified diagnoses and an unselected twin population showed that the risk of cancer in same- or different-sexed twins did not differ to that of singletons, with a few possible exceptions. Testicular seminomas, neurinomas and nonthyroid endocrine tumors were increased and colorectal cancers, skin tumors and leukemia were decreased among all, and preferentially in same-sexed twins. The observations of colorectal and testicular cancers are likely to have a biological basis and as one possibility, explanations could be sought in singletons of low birthweight.

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