

RESEARCH ARTICLE

Characteristics of 240 Chinese Father-child Pairs with Malignant Disease

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Abstract

To obtain a screening and early detection reference for individuals who have a family history of cancer on the paternal side, we collected and analyzed data from 240 pairs in which both fathers and their children were diagnosed with cancer. Disease categories of fathers and sons were similar to that of the general population of China, whereas daughters were different from general female population with high incidence of breast cancer and gynecological cancer. Sons were more likely than daughters to have the same type of cancer, or to have cancer in the same organ system as their fathers ($P < 0.0001$). Sons and daughters developed malignant diseases 11 and 16 years earlier than their fathers, respectively ($P < 0.0001$ for both sons and daughters). Daughters developed malignant diseases 5 years earlier than sons ($P < 0.0001$). Men with a family history of malignant tumors on the paternal side should be screened for malignancies from the age of 45 years, or 11 years earlier than the age of their fathers' diagnosis, and women should be screened from the age of 40 years, or 16 years earlier than the age at which their fathers were diagnosed with cancer. Lung cancer should be investigated in both men and women, whilst screening should focus on cancer of the digestive system in men and on breast and gynecological cancer (ovary, uterine and cervical cancer) in women.

Keywords: Cancer - family history - father - son - daughter - screening - early detection

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Introduction

The incidence of cancer is increasing worldwide, and concern for cancer prevention and early detection programs are growing amongst the general population – especially amongst people with a family history of cancer. Familial clusters of cancer patients may well serve as valuable population groups for epidemiological studies of cancer. These clusters could indicate the overall contribution of inherited genes as well as shared environmental factors that have a role in the development of malignant diseases. For instance, the siblings of long-term childhood cancer survivors are known to have an increased risk of cancer (Friedman et al., 2005). Siblings share genetic and environmental factors in the same way as parents and children. A family history of cancer in parents constitutes a risk factor for common malignancies, including, colon, prostate, and breast cancer (Johns et al., 2001; Kiciński et al., 2011; Tao et al., 2011) and a family history of cancer on the paternal side is known as a risk factor for several malignant diseases in children. For instance, there is a significant positive association between patients with lobular breast cancer and a paternal diagnosis of cancer (Ellberg et al., 2011). In addition, when considering that 90% of the sons of prostate cancer sufferers were concerned about their risks of inheriting the disease, and were therefore inclined to undergo screening

(Bratt et al., 1997), then it is clear that a diagnosis of cancer have significant psychological effects on first degree relatives.

Furthermore, familial clustering of prostate cancer and its association with an early onset of disease (before the age of 65 years) (Kiciński et al., 2011) suggests that there might potentially be a correlation between the development of malignant disease in fathers and their children, and that there might be some association between disease type and age of onset.

The aim of our study was to improve knowledge regarding the heritability of cancer. We assessed the probability of children developing the same type of cancer as their fathers, and the probability of children developing cancer at the same age as fathers with malignancy. In addition, we wanted to develop a reference for the screening and early detection of cancer in individuals who have a family history of malignancy on the paternal side. We analyzed data from 240 families in which both the father and at least one of his children developed malignant tumors.

Materials and Methods

Study population

We examined the family records of 15,000 people who visited the Department of Cancer Prevention, Cancer

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Table 1. Top Ten Malignant Diseases in 240 Father-child Pairs with Malignant Disease

No.	Fathers		Sons		Daughters		Sons and Daughters	
	Disease	Cases (%)	Disease	Cases (%)	Disease	Cases (%)	Disease	Cases (%)
1	Lung cancer	51(26.4)	Lung cancer	31(25.6)	Breast cancer	33(27.7)	Lung cancer	47(19.6)
2	Gastric cancer	33(17.1)	Hepatic cancer	17(14.0)	Lung cancer	16(13.4)	Breast cancer	33(13.8)
3	Esophageal cancer	29(15.0)	Colorectal cancer	15(12.4)	Ovary cancer	13(10.9)	Hepatic cancer	28(11.7)
4	Hepatic cancer	25(13.0)	Gastric cancer	14(11.6)	Hepatic cancer	11(9.2)	Colorectal cancer	25(10.4)
5	Colorectal cancer	20(10.4)	Esophageal cancer	10(8.3)	Colorectal cancer	10(8.4)	Gastric cancer	18(7.5)
6	Pharynx cancer	7(3.6)	Malignant lymphoma	8(6.6)	Thyroid cancer	7(5.9)	Esophageal cancer	13(5.4)
7	Pancreatic cancer	6(3.1)	Kidney and others	5(4.1)	Uterine cancer	5(4.2)	Ovarian cancer	13(5.4)
8	Prostate cancer	5(2.6)	Pancreatic cancer	3(2.5)	Cervical cancer	5(4.2)	Malignant Lymphoma	10(4.2)
9	Nasopharyngeal cancer	4(2.1)	Pharynx cancer	3(2.5)	Gastric cancer	4(3.4)	Thyroid cancer	9(3.8)
10	Malignant lymphoma	2(1.0)	Thyroid cancer	2(1.7)	Malignant lymphoma	2(1.7)	Cervical cancer	5(2.1)
	Sum	182(94.3)		108(89.3)		106(89.1)		201(83.8)

Table 2. Age Distribution of 240 Father-child Pairs with Malignant Diseases

Age	Fathers (%)	Sons (%)	Daughters (%)	Sons and Daughters (%)
<30	0 (0)	0 (0)	1 (0.8)	1 (0.4)
30-34	1 (0.5)	8 (6.6)	5 (4.2)	13 (5.4)
35-39	1 (0.5)	4 (3.3)	9 (7.6)	13 (5.4)
40-44	3 (1.6)	6 (4.9)	13 (10.9)	19 (7.9)
45-49	7 (3.6)	19 (15.7)	21 (17.6)	40 (16.7)
50-54	10 (5.2)	18 (14.9)	26 (21.8)	44 (18.3)
55-59	30 (15.5)	27 (22.3)	12 (10.1)	39 (16.3)
60-64	26 (13.5)	17 (14.0)	15 (12.6)	32 (13.3)
65-69	35 (18.1)	11 (9.1)	12 (10.1)	23 (9.6)
70-74	36 (18.7)	4 (3.3)	4 (3.4)	8 (3.3)
75-79	26 (13.5)	3 (2.5)	0 (0)	3 (1.3)
80-84	15 (7.8)	3 (2.5)	1 (0.8)	4 (1.7)
85-89	3 (1.6)	1 (0.8)		1 (0.4)
Sum	193	121	119	240

Hospital/Institute of the Chinese Academy of Medical Sciences for cancer screening between January 2009 and May 2012. We identified 240 father-son or father-daughter pairs with malignant disease. Patients were included in our study if (1) both the father and at least one child had a pathological diagnosis of cancer, (2) age of father and children was available at the time of diagnosis, (3) father was the biological father of the diagnosed child, (4) father and his child (ren) lived together for at least 18 years, and (5) mothers of children with malignant disease did not have cancer. This study was approved by ethical committee board of Cancer Hospital/Institute of the Chinese Academy of Medical Sciences.

Data analysis

Chi-square tests were used to evaluate the similarity of malignant diseases in fathers and children, whilst the age differences between fathers, sons, and daughters were analyzed with independent t-tests. Data analyses were carried out with SPSS software package, version 11.0 (SPSS Inc., Chicago, IL, USA).

Results

General information

Among the 240 father-child pairs from 193 families, 151 pairs consisted of a father and 1 child with cancer (among them, there were 75 sons and 76 daughters), and

42 families had a father and more than 1 child with cancer. Among these 42 families, 9 families had 2 daughters and 11 families had two sons with cancer, 17 families had 1 daughter and 1 son, 2 families had 3 daughters, 1 family had 3 sons and 2 families had 2 sons and 1 daughters with cancer. Taken together, there were 193 fathers and 240 children (121 sons and 119 daughters) in our research population. There was an almost equal distribution of sons and daughters among the 42 families in which more than 1 child was diagnosed with cancer and among the 151 families in which 1 child was diagnosed with cancer.

Incidence of malignant diseases

The incidence rate of malignant disease in fathers, sons, and daughters are shown in Table 1. Lung cancer was the most common malignancy in fathers. The 10 most prevalent cancers, found in 182 of the 193 fathers (94.3%), were: bronchial-lung cancer (n = 51, 26.4%), gastric cancer (n = 33, 17.1%), esophageal cancer (n = 29, 15.0%), hepatic cancer (n = 25, 13.0%), colorectal cancer (n = 20, 10.4%), pharyngeal cancer (n = 7, 3.6%), pancreatic cancer (n = 6, 3.1%), prostate cancer (n = 5, 2.6%), nasopharyngeal cancer (n = 4 cases, 2.1%), and malignant lymphoma (n = 2, 1.0%). According to data from the 2007 National Central Cancer Registry (NCCR), the 10 most prevalent malignant tumors in men and their proportion in the population were: bronchial-lung cancer (22.26%), gastric cancer (14.86%), hepatic cancer (13.11%), colorectal cancer (10.65%), esophageal cancer (8.80%), bladder cancer (3.45%), prostate cancer (3.21%), pancreatic cancer (2.60%), renal- and other tumors of urinary system (2.41%), and lymphoma (2.28%) (Chen,et al., 2012).

The most common malignancies and their proportion of the cancers amongst fathers enrolled in our study were similar to the NCCR 2007 data. Other common cancers (ranked in the second to the fifth position) were gastric, esophageal, hepatic, and colorectal cancer. The proportion of esophageal cancer amongst fathers in our study (15.0%) was higher than the NCCR 2007 data (8.8%). The order and proportion of gastric, hepatic, and colorectal cancer were similar to the NCCR 2007 data. The top 5 malignancies were found in 158 (81.9%) of the 193 fathers in our study.

The most common cancer amongst sons was also the same as the NCCR 2007 data. Malignancies ranked in the

second to the fifth position were also similar to the NCCR 2007 data, albeit with a different order. The top 5 diseases were found in 87 (71.9%) of the 121 sons.

According to NCCR 2007 data, the top 10 cancers amongst women were breast cancer (17.53%), lung cancer (13.88%), colorectal cancer (10.82%), gastric cancer (8.82%), hepatic cancer (5.65%), esophageal cancer (5.16%), cervical cancer (4.72%), uterine cancer (3.53%), ovarian cancer (3.48%) and thyroid cancer (3.40%) (Chen, et al., 2012).

Breast cancer was the most prevalent malignancy amongst the daughters in our study. The proportion of breast cancer was 27.3%, which was much higher than the NCCR 2007 data of 17.53%. The second most prevalent malignancy was lung cancer, and the proportion of lung cancer amongst the daughters more closely reflected the NCCR 2007 data. The prevalence of ovarian cancer (10.9%) was ranked third, and the proportion of this cancer in the daughters of our study was higher than that of the NCCR 2007 data (3.48%). On the other hand, esophageal cancer amongst the daughters was considerably lower (2.5%) than that of the NCCR 2007 data. The top 5 diseases – breast, lung, ovarian, hepatic, and colorectal cancer – were found in 69.7% of daughters (83 out of the 119 patients). Lung cancer, breast, and gynecological cancer (ovary, uterine, cervical cancer) accounted for 60.5% of cancers in daughters (72 out of 119).

The 10 most prevalent cancers in the total group was bronchial-lung cancer (19.6%), breast cancer (13.8%), hepatic cancer (11.7%), colorectal cancer (10.4%), gastric cancer (7.5%), esophageal cancer (5.4%), ovarian cancer (5.4%), malignant lymphoma (4.2%), thyroid cancer (3.8%), cervical cancer (2.1%). The disease with the highest incidence amongst the sons and daughters was lung cancer and the proportion of lung cancer (18.56%) was almost the same as the NCCR 2007 data. The second most common malignancy was breast cancer (13.8%), and the proportion of breast cancer amongst our group was considerably higher than the NCCR 2007 data since NCCR 2007 lists breast cancer (the proportion of breast cancer was 7.82%) as the 5th most common cancer in both sexes. Ovarian and thyroid cancer was ranked seventh (5.4%) and ninth (3.8%), respectively. These rates were higher than that reported in the NCCR 2007 data, and these cancers were not included in the NCCR 2007's 10 most prevalent cancers of both sexes. Bladder cancer, cerebral and neurological malignant tumors were relatively rare seen in the younger generation (Chen et al., 2012).

Category

The disease categories of fathers overlapped more with the disease categories of sons than with that of daughters. Among the 121 father-son pairs, 46 (38.0%) pairs had the same type of malignancy and 73 (60.3%) pairs developed diseases in the same organ system. Only 17 father-daughter pairs (14.3%) had the same type of malignancy and 34 pairs (28.6%) developed diseases in the same organ system. The probability of sons having the same malignancy and cancer in the same organ system as their fathers was much higher than that of daughters ($P < 0.0001$ for both type of disease and organ system).

Age

In total, for 20 consecutive years, 63.7% of fathers developed malignancies between 60 and 79 years of age, 66.9% of the sons developed malignant diseases between 45 and 64 years of age, and 62.2% of the daughters developed malignant diseases between 45 and 64 years of age. The most cases of two 5 years period of the fathers was between 65 and 74 years old and there was 71 cases (36.8%), it was between 50-59 years old for the sons and there was 45 cases (37.2%). For the daughters it was between 45-54 years old and there were 47 cases (39.5%) (Table 2).

The average age at diagnosis of malignant disease in fathers, sons, and daughters were 65.6 ± 10.4 , 54.7 ± 11.4 , and 51.3 ± 10.5 years of age, respectively. The median age of the fathers, sons and daughters were 66, 55, 50 years. The sons and daughters developed malignant diseases 11 and 16 years earlier than their fathers ($P < 0.0001$ for both sons and daughters). Daughters were diagnosed with malignant diseases 5 years earlier than sons ($P < 0.0001$).

The proportion of cases, during 5 years period exceeded 10 %, from the age of 45 years for sons and 40 years for daughters (Table 2).

Discussion

A study that surveyed 27,000 people reported that about 25% of the general population had first-degree relatives with malignancies (Ramsey et al., 2006). As there is an increase in the incidence of malignant disease worldwide, a significant proportion of the general population has a family history of cancer from the paternal side. Research studies that investigate families in which parents and children are diagnosed with similar types of cancer can provide clues for the molecular etiological exploration of certain malignancies (Breslow et al., 1996). Children whose parents are diagnosed with malignant diseases are thought to have a high risk for the same type of cancer, including colon, prostate, and breast cancer (Johns et al., 2001; Kiciński et al., 2011; Tao et al., 2011; Zhou, et al., 2011). The results from our study differ from previously published data on family clusters of cancer. We found that the broad disease profile in our group of patients was the same as that of the general population, and the conclusion can become reference for the screening and early detection of people with family history of their fathers from general population instead of specific population with family history of specific malignant diseases.

Sons and daughters with malignant diseases were equally distributed amongst the 193 families that we studied, suggesting that sons and daughters had the same probability of developing malignant diseases if their fathers were diagnosed with cancer. Therefore, our results suggest that the inheritance of cancer related genetic factors from the paternal side is almost equal for sons and daughters.

The 5 most prevalent cancers in the fathers and in the sons in our study were similar. The most important risk factors for lung and for hepatic cancer are smoking (Mucha et al., 2006) and hepatitis virus infection (Yuen, et al., 2009) respectively. Helicobacter pylori (HP) infection

and insufficient nutritional intake have been confirmed as major risk factors for gastric cancer (Conteduca et al., 1996; Li et al., 2012), whilst consumption of alcohol and smoking are important risk factors for esophageal cancers (Oze et al., 2011; Oze et al., 2012). On the other hand, the consumption of fruit and vegetables was shown to have a protective effect for esophageal cancer (Berretta et al., 2012). Colon cancer are thought to be related to diet and nutritional factors (Vagas et al., 2012) and diet related factors are also known to be important risk factors for the other 3 digestive system diseases that are listed among the top 5 malignant diseases (gastric, esophageal and hepatic cancer). Lung cancer was the most prevalent malignancy amongst sons in our study. Therefore, lifestyle factors such as smoking, drinking, and infectious diseases, such as hepatitis virus and HP infection, might be major risk factors for the development of cancer in father-son pairs. Preventative measures, such as refraining from, or relinquishing a habit of smoking and alcohol consumption, maintaining a healthy diet and taking precautions against hepatitis virus and HP infection, can thus be important strategies in limiting the risk of cancer in sons who have a family history of cancer on the paternal side.

Furthermore, our results show that the 5 most prevalent cancers in sons and the 3 most prevalent cancers in daughters were similar to that reported by the NCCR 2007 data. So, even though our patients had a hereditary background that differed from that of the general population, nonhereditary factors such as air pollution, life style changes including dietary changes, and psychological factors (a more competitive social environment) might contribute to an early onset of malignant disease amongst the younger generation. Our data were consistent with the findings of studies in prostate cancer and melanoma. Familial aggregation of prostate cancer was associated with earlier disease onset (before age 65) (Kiciński et al., 2011) whilst the median age of a diagnosis of invasive melanoma reduced by 11 to 16 years in successive generations (Goldstein et al., 1994). Our data corroborates these findings and we also show that children were diagnosed with cancer at a younger age than their fathers, even when fathers and children had completely different disease profiles. This is similar to the situation in the general population, and it supports the notion that sons or daughters with a family history of cancer should be screened for the early detection of malignancies according to the general population guideline with some special concern. Cancer screening in the younger generation should be started earlier.

In our study 38% of the sons suffered from the same cancer as their fathers and 60.3% of the sons developed cancer in the same organ system as their fathers. Only about 14.3% of daughters had the same disease as their fathers and less than one third of daughters developed diseases in the same organ system as their fathers. Therefore, with regards to the type of disease and organ system involved, sons shared more hereditary characteristics with their fathers than daughters. Men and women are known to have different malignant disease profiles and different sex chromosomes. Sons tend to have the same life style hence the same high risk factors such

as smoking and drinking because boys try to imitate their fathers (Fallot et al., 1976; Garmiené et al., 2006). This might explain the lack of overlap between cancer types and organ systems involved in fathers and daughters. In addition, these findings suggested that sons should pay more attention to the type of cancer and the organ system that is affected their fathers.

We suggest that sons with a family history of malignancy on the paternal side should undergo intensive screening for lung and digestive system cancer, and screening should commence earlier than the age at which their fathers were diagnosed with cancer.

The disease profile of the daughters in our study was different from that of the general female population and we found a high incidence of breast and gynecological cancers in our study group. Women with a family history of malignancy on the paternal side should focus on lung, breast, and gynecological cancers. The reasons for this are not clear and it requires further exploration. There is a significant positive association between lobular breast cancer and a father diagnosed with cancer (Ellberg et al., 2011) and daughters in our study had higher incidence of breast and gynecological cancers. Taken together, these findings suggest that endocrine factors might be involved in the mechanism underlying carcinogenesis in daughters. However, this notion needs further exploration.

The proportion of cases, during the 5 years period exceeded 10 %, from the age of 45 years for sons and 40 years for daughters. Daughters developed malignant diseases earlier than sons. This trend was also seen amongst men and women in the general population. Between the age of 20 and 55 years, women had higher age-specific incidence rates than men. However, from the age of 55 years, men had higher age specific incidence rates than women (Chen et al., 2012).

In China, cancer screening and early detection was initiated only in recent years. Most of the fathers and children in our study population were diagnosed when they already had middle to late stage cancer and they presented with symptoms and signs of disease at time of diagnosis. According to NCCR data, the incidence of age specific rate exceeded 200 per 10⁵ from 45 years old for the men. The sons in our study were diagnosed at a median age of 55 years. Therefore, we suggest that sons with a family history of malignant disease from the paternal side should start to screen for cancer from 45 years of age or at least 11 years earlier than the age at which their fathers were diagnosed with cancer.

On the other hand, NCCR data showed that the incidence of malignant disease among women began to increase significantly from 40 years age and female age specific incidence was near 200 per 10⁵ from 40 years old. Daughters in our study were diagnosed at a median age of 50 years. Therefore, Daughters with family history of cancer on the paternal side should be screened for cancer from 40 years of age or at least 16 years earlier than the age of their fathers' diagnosis.

Fathers and children share genetic, environmental and lifestyle risk factors for cancer. Our study investigated some of the characteristics of father-son and father-daughter pairs with cancers. Our finding can serve as

a reference for the screening and early detection of the population with a family history of cancer on the paternal side.

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