COMMON CANCERS SHARE FAMILIAL SUSCEPTIBILITY: IMPLICATIONS FOR CANCER GENETICS AND COUNSELING

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ABSTRACT

Background: It has been proposed that cancer is more common in some families than in others, but the hypothesis lacks population level support. We use a novel approach by studying any cancers in large 3-generation families and thus are able to find risks even though penetrance is low.

Methods: Individuals in the nation-wide Swedish Family-Cancer Database were organized in 3 generations and the relative risk (RR) of cancer was calculated to the persons in the third generation by the numbers of cancer patients in generations 1, 2 and 3.

Results: The RRs for any cancer in generation 3 increased by numbers of affected relatives, reaching 1.61 when at least 7 relatives were diagnosed. The median patient had 2 affected relatives, and 7.0% had 5 or more affected relatives with an RR of 1.46, which translated to an absolute risk of 21.5% compared to 14.7% in population by age 65 years. For prostate cancer, the RR was 2.85 with 4 or more affected family members with any cancer, and it increased to 14.42 with 4 or more concordant cancers in family members. RRs for prostate cancer were approximate equal (2.70 vs 2.85) if a man had 1 relative with prostate cancer or 4 or more relatives diagnosed with any cancer.

Conclusions: A strong family history of cancer, regardless of tumor type, increases cancer risk of family members and calls for mechanistic explanations. Our data provide tools for counseling of cancer patients with both low and high familiar risks.

INTRODUCTION

The absence of correlation of risk of most cancers between spouses, particularly those not related to tobacco smoking, suggests that familial cancers are mainly due to genetic causes [1]. However, the known genes explain a small proportion of the familial clustering and, consistently, a recent analysis of genome-wide association studies (GWASs) on 13 cancers could explain no more than 15 to 53% of the empirical familial risk [2, 3]. A further question is the sharing of familial risks between cancer sites. Data on many known cancer syndromes show pleotropic effects on multiple sites. For example, hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome), initially found in colorectal cancer families, was later shown to be associated with a high risk of endometrial cancers and a somewhat lower risk of at least half a dozen other cancers [4]. Similarly, BRCA1 and BRCA2 which were identified in breast and ovarian cancer pedigrees, are now known to predispose to at least five other tumors [5]. A review of Rahman on cancer predisposing genes listed 114 genes and only 39% were associated with cancer at a single site [6]. Even this figure is likely to be too high because the initial studies focus on a single cancer type.

Thus, despite an intense research effort in the past two decades, cancer predisposing genes seem to account for a small proportion of familial cancer, and the above GWAS analysis concluded that "most pairs of cancers…are unlikely to have strong genetic correlations" [3]. Population-based family studies from Utah, Iceland and Sweden have reported results on different (i.e., discordant) sites , and the Utah and the Icelandic data covered more than 2 generations [7-10]. In the Utah dataset, associations were estimated for 36 different cancer sites. Prostate cancer had most interactions with other cancer sites, and its relative risks were increased in the first-, second-, and third-degree relatives when probands diagnosed with 11 different cancer sites [7].According to the Icelandic data, 20 discordant cancer pairs were significant of 351 pairs tested and the relative

risks ranged from 1.1 to 1.5 among second degree relatives [9]. Based on the Swedish study on discordant cancers, we concluded our large study on 33 cancer sites: “Within the present sample size limits, we found no evidence of an overall susceptibility to cancer” [10].

The issue of a general susceptibility to cancer does not appear to be settled because cancer syndromes often manifest multiple and diverse cancers while population-level family studies show far lower risks, if any, in discordant compared to concordant familial cancers. A limitation in published family studies has been a focus on pairs of selected cancers (A and B). Such a design would perform well if a genetic factor causes a reasonable risk (reasonably high penetrance) in cancers A and B but the statistical power would be low if a gene or a set of genes cause a lower risk (low penetrance) of many cancers. We present here a novel approach of analyzing cancers in 3 generations and considering risks for any cancer and for the most common individual cancers. By combining data on first, second and third degree relatives we could identify families with large numbers of affected individuals. The data are relevant to genetic counseling, which understandably focuses on high risk syndromes and families. More broadly, our findings are useful in the general oncology practice, because they help physicians answer very common questions relating to the familial risks “caused by” malignancies found in the patients’ extended families.

PATIENT AND METHODS

The Swedish Family-Cancer Database (FCD) was used to estimate familial cancer risks. It was formed by merging data from the Multigeneration Register, the Swedish Cancer Registry and several other databases [11-13]. The individual linkages in the databases were based on the unique national identification number. The latest update of the FCD contains information until 2012, including 15.7 million individuals and 1.8 million medically verified cancer cases. The

FCD is composed of children born from 1932 onwards and their biological parents. The available offspring-mother-father triplets were used to create pedigrees comprising of first-degree relatives (parents and siblings), second-degree relatives (grandparents, uncles and aunts) and third-degree relatives (cousins). In the present study, individuals born before 1932 for which no parental linkage was available were considered as the first generation. Individuals born between 1932 and 1951 were defined as the second generation. Offspring of the second generation were defined as the third generation. A total of 1,846,840 third generation individuals were enrolled into the study as index individuals who were used for calculating the cancer risks and the number of their first-degree, second-degree and third-degree relatives affected with cancers was regarded as probands who was used to define the different family histories.

Among the index individuals 41,106 cancers were diagnosed. A 4-digit diagnostic code, the 7th version of International Classification of Disease (ICD-7), was used to identify the cancer site. To estimate individual cancer risks for any cancer in the family, the 33 most common cancers were taken into consideration, including the upper aerodigestive tract, esophagus, stomach, small intestine, colorectum, anus, liver, pancreas, nose, lung, breast, cervix, endometrium, uterus, ovary, other female genital, prostate, testis, other male genital, kidney, urinary bladder, melanoma, skin, eye, nervous system, thyroid gland, other endocrine glands, bone, connective tissue and hematopoietic tissue (non-Hodgkin's lymphoma, Hodgkin's disease, myeloma and leukemia). In addition, tobacco related cancers were defined as lung, upper aerodigestive tract, kidney, and bladder cancers. Due to the small case numbers, the latter three were merged into one group termed 'other tobacco related cancers'. For the most common cancers of the breast, prostate, colorectum and lung, risks for concordant cancers in the family were also investigated. Since breast cancer is sex-specific, only female cases among the index individuals were taken into account.

Based on the index individuals, person-years and cases were calculated stratifying for different family histories (i.e., numbers of relatives with cancer) and potential confounders such as sex, age, calendar period, residential area, and socioeconomic status. Considering these stratification variables as covariates, a Poisson regression model was employed to estimate familial risks. Thereby, relative risks (RRs) in terms of incidence rate ratios and their 95% confidence intervals (CIs) were calculated for different family histories [14]. Familial risks were found to be significantly increased or decreased, respectively, if the 95% CI did not include 1.00. Trend tests were performed to assess whether RRs increased by the number of the affected relatives. P-values less than 0.05 were considered statistically significant.

All statistical analyses were performed using SAS software version 9.3. The Lund University regional ethics committee approved the study.

RESULTS

The birth years of cancer patients identified in the 3 generations probands under study are shown in Fig. 1. The probands among 3 generations had 468,549, 367,642 and 48,730 cancers, respectively. The risk was calculated to the third generation depending on the numbers and types of cancers in the proband generations; the birth years of cancer patients in the 3 generations show maximal births in years 1920, 1943 and 1964, respectively.

Table 1 shows the distribution of family sizes and cancer cases among the third generation, with a minimum of less than 5 (with missing parental or grandparental information) and a maximum of more than 60. The proportion of cancer patients among the 1,846,840 individuals in the third generation appears not to depend on the family size.

Table 1 Family size and cancer cases distribution among the third generation

	Family size													
	<=5	6-10	11-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	>60	Total
Cancer cases	5,430	9,439	10,150	7,350	4,211	2,202	1,150	579	279	149	86	32	49	41,106
index individuals	254,706	385,914	451,620	339,970	198,819	104,858	53,980	27,741	14,070	7,238	3,927	1,975	2,022	1,846,840
Percent	2.13%	2.45%	2.25%	2.16%	2.12%	2.10%	2.13%	2.09%	1.98%	2.06%	2.19%	1.62%	2.42%	2.23%

Cancer risks in the third generation are shown in Table 2 by the number of cancer patients in generations 1, 2 and 3. Risks were compared to those without relatives with cancer. For men the highest RR was 1.46 when 7or more relatives were diagnosed with cancer; for women the highest RR was 1.72 when 7 or more relatives were diagnosed. In data on combined sexes, the RRs reached 1.61 when at least 7 relatives were diagnosed. The RRs increased by numbers of affected relatives (all trend test p-values < 0.0001). The median patient in the third generation had 2 affected relatives and 7.0% had 5 or more affected relatives.

Table 2 Familial risks for any cancer among the third generation

Cancer cases in the family	Male			Female			Total		
	N[1]	RR[2]	95%CI[3]	N	RR	95%CI	N	RR	95%CI
0	2605	ref[4,5]	--	3721	ref[5]	--	6326	ref[5]	--
1	4334	**1.07**	(1.01-1.13)	6362	**1.10**	(1.04-1.15)	10696	**1.08**	(1.04-1.13)
2	4151	**1.11**	(1.05-1.18)	6172	**1.17**	(1.11-1.23)	10323	**1.14**	(1.10-1.19)
3	2793	**1.14**	(1.08-1.21)	4282	**1.23**	(1.16-1.30)	7075	**1.19**	(1.14-1.24)
4	1578	**1.28**	(1.19-1.37)	2247	**1.27**	(1.19-1.36)	3825	**1.28**	(1.21-1.34)
5	725	**1.36**	(1.24-1.49)	976	**1.29**	(1.19-1.41)	1701	**1.32**	(1.24-1.41)
6	290	**1.44**	(1.26-1.65)	424	**1.44**	(1.27-1.63)	714	**1.44**	(1.31-1.58)
7+	166	**1.46**	(1.23-1.74)	280	**1.72**	(1.48-2.00)	446	**1.61**	(1.43-1.82)

1: N=Number of cancer cases among the index individuals;
2: RR=Relative risk;
3: CI=Confidence interval;
4: ref=Reference;
5: Trend test p-value **< 0.0001**.

In Table 3 we show results for specific cancers in four ways of defining proband cancers, on top by considering any cancer and in the bottom by considered only concordant cancer. In addition any cancer excluding concordant cancer and any cancer excluding concordant cancer and cancer syndrome were also taken into consideration.

For lung cancer the RRs were significantly increased when relatives were diagnosed with concordant cancer only (trend test p-value < 0.0001). For colorectal, prostate and breast cancers, most comparisons were significant and all the trend tests were statistically significant; For prostate cancer, when probands had any cancer, the RR increased to 2.85 with 4 or more affected family members, and it increased to 14.42 with 4 or more concordant cancers in family members. For breast cancer, the RR increased to 1.48 with 4 or more affected family members with any cancer, and it increased to 3.77 with 4 concordant cancers in family members.

Table 3 Familial risks for colorectal, lung, prostate and breast cancers among the third generation for different family histories

Cancer cases in the family		Colorectal cancer			Lung cancer			Prostate cancer			Breast cancer		
		N[1]	RR[2]	95%CI[3]	N	RR	95%CI	N	RR	95%CI	N	RR	95%CI
Any cancer	0	326	ref[4]	--	114	ref	--	85	ref	--	1063	ref	--
	1	552	1.09	(0.92-1.29)	195	1.11	(0.85-1.44)	176	**1.38**	(1.02-1.86)	1801	1.09	(0.99-1.19)
	2	572	**1.25**	(1.05-1.47)	182	1.19	(0.91-1.55)	183	**1.70**	(1.26-2.28)	1785	**1.20**	(1.09-1.31)
	3	372	**1.23**	(1.03-1.48)	117	1.18	(0.88-1.59)	107	**1.62**	(1.17-2.25)	1269	**1.29**	(1.17-1.43)
	4+	373	**1.44**	(1.20-1.73)	111	1.30	(0.96-1.75)	164	**2.85**	(2.11-3.86)	1248	**1.48**	(1.33-1.63)
P-value for trend test				**< 0.0001**			0.08			**< 0.0001**			**< 0.0001**
Any cancer (excluding concordant cancer)[5]	0	326	ref	--	114	ref	--	85	ref	--	1063	ref	--
	1	619	1.12	(0.95-1.33)	203	1.10	(0.84-1.42)	233	**1.66**	(1.27-2.17)	2094	**1.14**	(1.05-1.25)
	2	547	**1.21**	(1.02-1.44)	187	1.24	(0.95-1.61)	150	**1.46**	(1.09-1.94)	1782	**1.22**	(1.11-1.33)
	3	317	1.20	(0.99-1.45)	102	1.12	(0.83-1.51)	92	**1.65**	(1.20-2.27)	1047	**1.24**	(1.12-1.38)
	4+	265	**1.33**	(1.08-1.63)	84	1.17	(0.85-1.62)	79	**2.02**	(1.45-2.81)	748	**1.27**	(1.13-1.42)
P-value for trend test				**0.0047**			0.28			**0.0007**			**< 0.0001**
Any cancer (excluding concordant cancer and cancer syndrome)[6]	0	326	ref	--	--	--	--	--	--	--	1063	ref	--
	1	639	1.14	(0.96-1.34)	--	--	--	--	--	--	2142	**1.15**	(1.05-1.25)
	2	532	1.19	(1.00-1.41)	--	--	--	--	--	--	1762	**1.21**	(1.11-1.33)
	3	320	**1.26**	(1.04-1.52)	--	--	--	--	--	--	995	**1.22**	(1.10-1.35)
	4+	241	**1.30**	(1.05-1.59)	--	--	--	--	--	--	689	**1.25**	(1.11-1.40)
P-value for trend test				**0.0059**			--			--			**< 0.0001**
Concordant cancer	0	326	ref	--	114	ref	--	85	ref	--	1063	ref	--
	1	467	**1.61**	(1.37-1.88)	115	**1.59**	(1.22-2.07)	223	**2.70**	(2.04-3.59)	1849	**1.65**	(1.51-1.80)
	2	85	**2.41**	(1.85-3.13)	17	**2.45**	(1.46-4.12)	91	**6.53**	(4.67-9.13)	387	**2.25**	(1.97-2.58)
	3	19	**5.54**	(3.34-9.22)	1	1.73	(0.23-12.87)	17	**7.49**	(4.15-13.52)	71	**3.24**	(2.45-4.27)
	4+	4	**9.00**	(3.05-26.59)	0	--	--	6	**14.42**	(5.64-36.85)	12	**3.77**	(1.95-7.27)
P-value for trend test				**< 0.0001**			**< 0.0001**			**< 0.0001**			**< 0.0001**

1: N=Number of cancer cases among the index individuals;
2: RR=Relative risk;
3: CI=Confidence interval;
4: ref=Reference;
5: Family members who had the same cancer with the third generation cancer cases were excluded;
6: For colorectal cancer, cancer syndrome was endometrium cancer; for breast cancer, cancer syndrome was ovary cancer.

Smoking is a well-known environmental cause of familial clustering of cancer, and we thus assessed the familial risk of lung cancer and other tobacco related cancers when family members were diagnosed with any smoking related cancers (Table 4). Most of the RRs were significant and the trend tests were highly significant.

Table 4 Familial risks for tobacco related cancers among the third generation

Tobacco related cancer cases in the family	Lung cancer			Other tobacco related cancers			Tobacco related cancers		
	N[1]	RR[2]	95%CI[3]	N	RR	95%CI	N	RR	95%CI
0	471	ref[4]	--	1413	ref	--	1884	ref	--
1	197	**1.40**	(1.16-1.68)	473	1.12	(0.99-1.27)	670	**1.19**	(1.07-1.32)
2+	51	**1.78**	(1.29-2.46)	123	**1.46**	(1.16-1.82)	174	**1.54**	(1.27-1.86)
P-value for trend test			**< 0.0001**			**0.0012**			**< 0.0001**

1: N=Number of cancer cases among the index individual;
2: RR=Relative risk;
3: CI=Confidence interval;
4: ref=Reference.

DISCUSSION

In taking family histories and in advising concerned individuals from cancer families the physician frequently faces a problem if the pedigree shows many diverse cancers which do not fit into any of the known cancer syndromes. There is no unambiguous scientific evidence demonstrating the existence of an overall susceptibility to many cancers. Some supporting evidence is derived from cancer syndromes and known cancer predisposing genes which manifest cancers at many sites [6]. However, known cancer syndromes account for a small share of all cancers and the GWAS based approach on 13 different sporadic (i.e., not hereditary) cancers provided genetic evidence against genetic sharing between pairs of cancers [3]. Family studies from Utah, Iceland and Sweden have arrived at an essentially similar conclusion that pairwise analysis of cancer sites fails to support the hypothesis of an overall general susceptibility to cancer [7-10]. The present results contradict such conclusions as they provide population level evidence of predisposition to diverse common cancers. An important limitation of the present study is that the third generation had reached a maximal age of 65 years by the end of the follow-

up in year 2012 and most cancers were diagnosed at the 50s. As the median age of cancer diagnosis in Sweden is 70 years, a large proportion of the third generation had not entered the risk age for cancer.

The present approach is novel in considering families in 3 generations and, instead of a pair-wise analysis, it considers clustering of any cancers in the families. The approach was devised after considering the emerging knowledge of the germline genetic architecture of cancer, which is characterized by rare high-and medium-risk genes and numerous low-risk genes, detected by GWAS [15]. An illustrative point is the genetic architecture of prostate cancer, for which medium-risk genes account for a few percent while low-risk genes/loci account for 39 % of the familial clustering [16]. Thus, considering familial cancer in 3 generations and multiple relatives has the advantage that the threshold for penetrance is lowered.

The present data showed that the median individual in the third generation had 2 affected family members and his risk was 1.14 for any cancer. Furthermore, 7.0% had at least 5 affected relatives and their risk was about 1.46. To translate the latter figure into an absolute risk, the cumulative risk of cancer by 65 years (matching the maximal age in the present third generation) for combined sexes was 14.7 % in Sweden [17]; thus the RR of 1.46 would lead to an absolute risk of 21.5%. Looking at specific cancers, when having the same number of relatives affected with any cancer, the RR of prostate cancer was much higher than the overall RR (1.38 vs 1.08, 1.70 vs 1.14, 1.62 vs 1.19, 2.85 vs 1.28). Since 715 cases were diagnosed with prostate cancer, which accounted for a very small proportion of the third generation cancer patients (the total number of 41,106 cases), the higher RRs of prostate cancer did little contribution to the overall RRs. That could interpret familial risks for any cancer were not as high as prostate cancer; the risk of

prostate cancer risk was approximately equal (2.70 vs 2.85) if a man had 1 relative with prostate cancer or 4 or more relatives diagnosed with any cancer.

Although the present data do not provide direct insight into possible mechanisms, a large number of cancer predisposing genes are tumor suppressors [6]. A number of tumor suppressor genes are involved in DNA repair, guarding the integrity of the genome, or in other essential cellular processes, and it would be easily understandable that damage in such genes would promote cancers in many tissues; these processes have been coined as 'hallmarks of cancer' [18-21]. Furthermore GWASs have identified genomic locations which contribute to susceptibility of numerous cancers, including chromosome 8q24 next to the MYC gene and 5p next to the TERT gene [2, 22, 23]. However single nucleotide polymorphisms (SNPs) in these loci are largely specific to individual cancers but their clustering next to the important effector genes is thought to signal shared mechanisms. The complex regulation of these loci is not fully understood but they may contribute to shared susceptibility to multiple cancers. The recently detected 'super enhancers' are key regulatory elements, which promote oncogene transcription in many cancers and would provide another mechanistic rationale to the present findings [24, 25].

In conclusion, this nation-wide study on families spanning a century provided compelling evidence that there indeed is a general susceptibility to cancer. The results are weighted by common cancers – because they are more common they are more prominent in statistical analyses - and whether the overall susceptibility applies to all cancer needs to be resolved in future studies. The data provided herein provide tools for genetic counseling of "regular" patients with multiple cases of cancer in their family but lacking a clear-cut hereditary predisposition. Moreover, the present data help place cancer risk in high risk families into their correct context. Future

challenges include molecular identification of the underlying causes of familial accumulation as described here.

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CONFLICTS OF INTEREST DISCLOSURE

Yes there are potential competing financial interests. A.H. is shareholder in Targovax ASA. A.H. is employee and shareholder in TILT Biotherapeutics Ltd.

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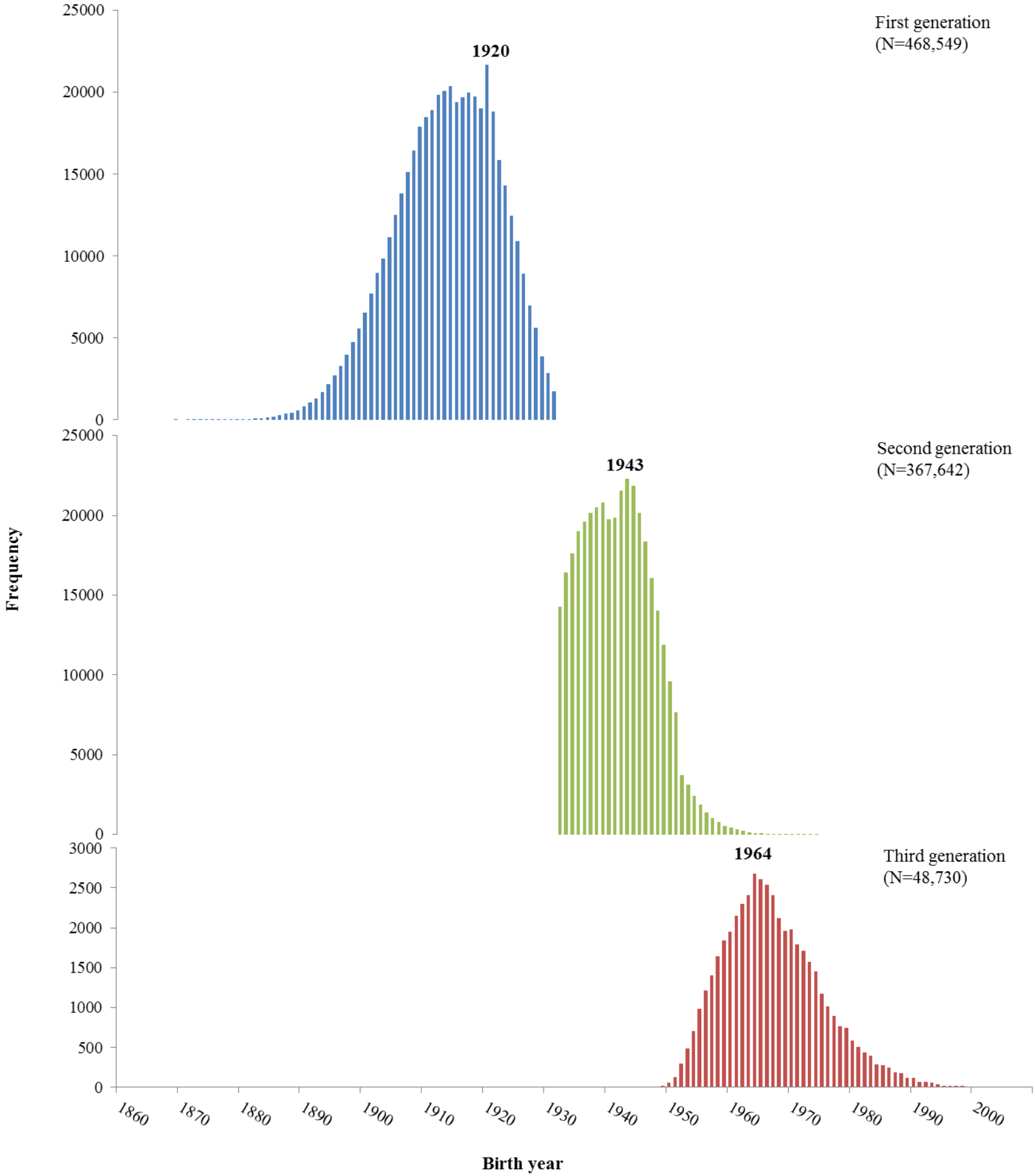
LEGENDS TO FIGURES

Fig. 1. Birth year distribution of cancer patients in the 3 generations probands. The year of maximal number of cases is shown on top of each distribution.


First generation
(N=468,549)
1920
Second generation
(N=367,642)
1943
Third generation
(N=48,730)
1964
Frequency
Birth year
25000
20000
15000
10000
5000
0
3000
2500
2000
1500
1000
500
1860
1870
1880
1890
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000