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Accuracy of family history of cancer: clinical genetic implications

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Family medical history is the cornerstone of clinical genetic diagnosis and management in cases of familial cancer. The soundness of medical decisions can be compromised if reports by the family on affected relatives are inaccurate. Although very time consuming, family medical histories are therefore routinely verified. To investigate whether such verification is clinically justified, we retrospectively analysed the accuracy of a consecutive series of 383 tumour reports from counsellees on 120 families in our clinic. We evaluated these families for the impact of verification on clinical genetic diagnosis and management. Accuracy according to cancer type showed marked variation, ranging from 93% and 89% for breast cancer and colorectal cancer, respectively, to 42% and 37% for extra-colorectal alimentary tract cancer and uterine cancer. Accuracy was related to the degree of kinship of the affected relative, but not to age and gender of the counsellee, nor to the reason for referral or personal history of cancer. Age at diagnosis and multiple primary tumours were reported accurately in 97% and 94% of cases, respectively. In six out of 120 families verification data changed clinical genetic management, in five of these the genetic risk was reduced. Although verification of all reported cancer cases in a family remains the 'gold standard' for clinical as well as research purposes, verification of reports on breast cancer can be limited without seriously compromising medical decision making. In cases where verification is impossible because medical records are unavailable, findings from studies such as ours may help in interpreting family histories.
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Introduction

A large proportion of clinical genetic activity (33% in our centre) is now dedicated to the analysis of families suspected of hereditary cancer. Family history of cancer plays a central role in this analysis. Unfortunately, a family's details of its cancer history are not necessarily accurate and may lead to wrong clinical decisions and counselling if they are left unverified. However, verification is time-consuming and a rapidly growing burden on the clinic. Therefore, it would be helpful if verification could be minimised without compromising the soundness of clinical genetic decisions. Only a few studies have addressed the accuracy of the family's record

of cancer, mainly when it was collected for epidemiological purposes.[1–11] Studies on the accuracy of a family's history of cancer as obtained by methods commonly used in family cancer clinics are rare[12,13] In this retrospective study we investigated the accuracy of the family's history of cancer, in the setting of the familial cancer clinic in Groningen.

Material and methods

General procedure for recording and verifying a family's history

Each counsellee referred to the Department of Medical Genetics in Groningen in respect of the history of cancer in the family is sent a form at least 4 weeks before first visiting the Department. On that form, the counsellee is asked to fill in family details (number and type of all first, second and most third degree relatives; names, dates of birth and death of first and second-degree relatives; type of cancer and age at

tumour diagnosis in all relatives). A leaflet which accompanies the form encourages the counsellee to supply detailed information on cancer cases in the family, excluding metastases. The form is returned before the first visit to the Department and a pedigree is drawn up based on the information given. On the first visit, details of the family cancer history are discussed with the counsellee by a clinical geneticist, who explains (again) the difference between primary tumours and metastases. As a result, a number of tumours may be reclassified during that visit as (probable) metastases. Details of the family's history of cancer are subsequently verified, for which a written consent has to be obtained from each living relative on whom information must be verified. In respect of deceased relatives, the doctor who treated them decides whether or not to supply the information. The sources for verification are the patient's medical records (including pathology reports), which are stored for the legal minimum of 10 years after the last clinical contact and may be destroyed after that period. Dutch academic hospitals have a general policy of keeping medical records for 115 years after the patient's date of birth. Only physicians who signed the death certificates have legal access to them for clinical purposes (other rules apply to epidemiological studies). As it is virtually impossible to identify and contact these physicians years after the certificates have been filed, death certificates in the Netherlands are useless for verification purposes. For practical reasons, negative histories of cancer in relatives are almost never verified.

Retrospective family history verification study

A consecutive series of 139 counsellees from 129 families referred to the Department between 1977 and 1997 in connection with family cancer history was included in this study. Counsellees whose family histories had already been verified by other institutes were excluded. If a family was already included in the study, new counsellees from that family were excluded unless they were only distantly related to the contacts already included and had collected details on their family medical history independently of the other contacts by having been in touch with different relatives for that purpose (16 counsellees from 6 families fell within this category). In 120 of the 129 families included, reported histories of cancer had been verified.

Data on the following items were retrospectively collected from the Department's records assembled by these consultands and their families and stored in a computer database (dBase IV, © Borland Inprise, Scotts Valley, CA, USA) under:

(a) family identification no;

(b) reported primary tumour types in the contacts and their relatives;

(c) type (eg parent) and degree of kinship with those relatives (eg 1st);

(d) reported ages at tumour diagnosis (categories within 5-year intervals);

(e) clinical diagnosis where the family's history had been taken at face value (and before any additional physical examination/laboratory testing);

(f) outcome of verification of the reported tumours (type, age at diagnosis);

(g) reasons for non-verification; and

(h) clinical diagnosis directly after verification (and before any additional physical examination/laboratory testing).

In addition, the following items were included because they were thought to be possible confounders in the statistical analysis:

(i) gender of the contact;

(ii) age of the contact;

(iii) whether or not the contact had a personal history of cancer, and if so what type;

(iv) reason for referral; and

(v) number of years since diagnosis of each reported tumour.

The family's history of a particular cancer was considered accurate if both organ and disease type (ie cancer) were correct. If the medical history included a wider category (eg 'leukaemia') rather than a specific diagnosis (eg CML), the report was considered accurate if the confirmed diagnosis fell within that wider category. Reported age at diagnosis was considered accurate if it differed less than 5 years from the true age.

The χ^2 test for heterogeneity was used to test for statistical differences in accuracy between the kinship–tumour type of class for each of the above parameters. Where sample sizes were too small for the χ^2 test (breast, ovarian and colorectal cancer groups) Fischer's exact test was used. The χ^2 test for trends was used to look for increasing or decreasing accuracy with increasing or decreasing degrees of kinship. *P* values below 0.05 were considered statistically significant. All tests were performed using the SPSS computer program (version 6.1, © Statistical Package for the Social Sciences, Inc, Chicago, IL, USA).

Results

A total of 886 tumours had been reported by the 129 families. Of these reported tumours, 383 (43%) in a total of 120 families had been verified (results shown in Table 1). Although we had recorded the specific type of relative within each degree of kinship (eg siblings, parents and children within the first degree category), the sample sizes in each of these subcategories were too small to be used for statistical analysis.

Table 1 Accuracy of the family history depending on degree of kinship and tumour type

Type of cancer:	Degree of kinship					All degrees	P value for heterog./trend
	0	1	2	3	4		
	% accurate of (n) reported tumours						
Breast	100 (15)	94 (69)	90 (31)	75 (8)	100 (2)	93 (125)	0.25/n.a.
Colorectal	100 (14)	91 (33)	100 (15)	57 (7)	60 (5)	89 (74)	0.006/n.a.
Ovarian	100 (5)	67 (15)	60 (5)	50 (2)	100 (1)	71 (28)	0.52/n.a.
Other	85 (26)	70 (63)	52 (42)	44 (9)	38 (16)	63 (156)	0.006/<0.0001
All types	95 (60)	91 (180)	79 (93)	68 (26)	60 (24)	78 (383)	<0.0001/<0.0001

Degree of kinship: 0: the counsellees themselves; 1: children, siblings and parents; 2: grandchildren, grandparents, nephews, nieces, aunts and uncles; 3: sibling's grandchildren, cousins, great-grandparents' and grandparents' siblings. For details on the category cancer type 'other', see results section. Accurate: reported disease type (malignant) and organ type both confirmed. Fischer's exact test was used to test for differences (heterog: heterogeneity) in the categories breast cancer, colorectal cancer and ovarian cancer, because of smaller sample sizes. In these categories

We therefore only present the data on the degree of kinship. Numbers of reported tumours in the category 'other' in Table 1 were also relatively small. Therefore, differences of accuracy between different degrees of kinship were not calculated for the individual tumour types in this category. When *all* degrees of kinship were pooled, significant heterogeneity ($P < 0.0001$) was observed for the accuracy of the reported tumour types/subcategories: accuracy for breast cancer was 93%, for colorectal cancer 89%, central nervous system cancer 88%, respiratory tract cancer 78%, urogenital tract cancer 78%, ovarian cancer 71%, haematolymphoid malignancies 64%, extra-colorectal alimentary tract cancer 42%, uterine cancer (including uterine cancer not further specified, endometrial cancer and cervical cancer) 37% and the remainder 63%.

Accuracy of reported cases was not related to the gender of the counsellee ($P = 0.59$), their age ($P = 0.34$), personal history of cancer ($P = 0.62$), time since tumour diagnosis ($P = 0.1$) and early age at diagnosis ($P = 0.50$). If the reason for referral was suspected hereditary breast–ovarian cancer, accuracy of reports on breast ($P = 0.72$) and ovarian cancer

($P = 1.0$) were not significantly different from those in families which had been referred for suspected other tumour syndromes. If the reason for referral was suspected hereditary non-polyposis colorectal cancer, accuracy of reports on colorectal ($P = 0.36$) and uterine cancer ($P = 0.80$) were not significantly different from those in families who had been referred for suspected other tumour syndromes.

In 72% of the reported tumours, age at diagnosis was given. This depended significantly on the degree of kinship: ages were reported more often in closer relatives ($P < 0.001$). Of these reported ages, 97% were correct (dependence on degree of kinship could not be calculated due to the small number of incorrectly reported ages). Of the 32 reports on multiple primary tumours, the fact that they were indeed multiple was accurate in 94% of cases (dependence on degree of kinship could not be calculated due to the small number of these reports).

Differences were observed between the syndrome diagnosis at the family level (based solely on family history) before and after verification in 17 out of 120 families (14%), listed in Table 2. In six of those families (c, g (3x), h and i), ie

Table 2 Families with differences in syndrome diagnoses before and after verification of the family history

Diagnosis before verification	Diagnosis after verification	No.
a) Hereditary breast-ovarian cancer (HBOC)	probably[a] HBOC	4
b) Suggestive[b] of HBOC	HBOC	2
c) Suggestive[b] of HBOC	not suggestive of any inherited cancer predisposition	1
d) Hereditary breast cancer (HBC)	probably[a] HBC	2
e) HBC	suggestive[b] of HBC	1
f) Hereditary non-polyposis colorectal cancer (HNPCC)	probably[a] HNPCC	2
g) Familial clustering of cancer	not suggestive of any inherited cancer predisposition	3
h) Familial clustering of acute lymphocytic leukaemia (ALL)	non-familial ALL	1
i) Possibly basal cell naevus syndrome[c]	basal cell naevus syndrome	1

Each syndrome diagnosis (at the family level) shown is based solely on family history (either unverified or verified), which is the basis for further medical decisions on eg DNA testing and follow-up. Diagnosis before verification reflects diagnosis if family history had been believed to be completely accurate.
Differences between diagnosis before and after verification were observed in 17 out of 120 families. These differences were clinically important with regard to medical decision making in only six families (c, g (3×), h and i).
[a]Probably HB(O)C/HNPCC refers to the post-verification situation in which the clinical diagnosis would have been HB(O)C or HNPCC if the family history was assumed to be accurate. However information could not be collected on all relevant cases in the family (required for formal diagnosis).
[b]Suggestive of HBC means that although formal criteria for HBC have not been met (at least three verified breast cancer cases in two successive generations, one of the affected relatives being a first-degree relative of the other two – second-degree relative counts as first-degree in case of transmission through the paternal line), several facts point towards the HBC diagnosis, eg multiple early-onset primary breast cancer.
[c]Possibly basal cell naevus syndrome refers to the fact that family history was suggestive, but not detailed enough to make the diagnosis.

5% of the total number of families, this difference led to a change in indications for DNA testing, counselling and follow-up. In five out of six cases it meant a decrease in genetic risk; in one case (family i) it resulted in an increase.

Non-verified cases included 503 tumours or 57% of the total number of reported tumours. No effort to obtain written consent and subsequently to try to verify cases was made in 71% of these cases because

(a) it was certain that the files had been destroyed;

(b) counsellees were not in touch with the relatives concerned, so that no consent could be obtained;

(c) the reports concerned relatives from a branch of the family not of interest to the genetic investigation; or

(d) the reported cases were late-onset common type tumours in distant relatives not likely to be of interest in respect of referral.

Of the remaining 29%, written consent was obtained, but no information could be retrieved in 16% of cases. Written consent was asked for, but not given in 9% of cases. In the remaining 4% the reason for non-verification could not be found in our records.

Discussion

Our data show that the accuracy of a family's history of cancer, taken from a family cancer clinic, depends primarily on tumour type and degree of kinship, but not on age and gender of the counsellee, nor on the reason for referral, nor on a personal history of cancer. Most of the published studies reported similar relations between accuracy and tumour type or degree of kinship (Table 3). The low accuracy of reports of uterine cancer we observed, important because of its relevance to hereditary non-polyposis colorectal cancer diagnosis, confirms earlier observations of 25–40% accuracy rates.[11,14] Reported ages at diagnosis and reports on multiple

Table 3 Accuracy of family histories of cancer: review of published data

All tumours combined Degree of kinship			Breast	Colorectal	Ovarian	
1st	2nd	3rd	all	all	all	Comment and references
Percentage accurate of (n) reported cases						
91 (180)	79 (93)	68 (26)	93 (125)	89 (74)	71 (28)	This study
84 (216)	71 (174)	71 (73)	91 (157)	88 (79)	–	Families referred to family cancer clinic, FH taken by questionnaire, verified by MR[12]
86 (n.r.)	78 (n.r.)	59 (n.r.)	95 (n.r.)	–	–	Families referred to family cancer clinic, FH taken by questionnaire, verified by MR/DC/CR[13]
78 (32)[b]	70 (54)[b]	–	100 (5)	100 (5)	100 (2)	Case (ES) study, FH taken by mailed questionnaire + PI, verified mainly by DC[9,19]
85 (252)	67 (165)	–	98 (59)	87 (47)	57 (7)	Case (GLI) study, FH taken by PI (multiple relatives), verified by MR+DC[11]
–	–	–	57 (51)	52 (46)	27 (11)	Case (COL)-control study, FH taken by PI, confirmed by GDB/CR[10,14]
n.r. (230)	–	–	>88 (n.r.)	>88 (n.r.)	–	Case (CBT)-control study, FH taken by PI, verification method n.r.[5]
–	88 (2090)[c]	–	93 (349)	–	–	Case (LW) study, FH taken by PI (proband+parent), verified by MR+DC[1]
–	88 (100)[c]	–	–	–	–	Case (Mix)-control study, FH taken by mailed questionnaire, verified by MR+DC[3]
–	–	–	92 (97)	–	–	Case (BR)-control study, FH taken by PI, verified by MR[8]
88 (98)	72 (76)	–	–	–	–	Case (S) study, FH taken by PI, verified by MR+DC[6]
85–86[a] (n.r.)	20–36[a] (n.r.)	–	–	–	–	Case (TC)-control study, FH taken by unknown method, verified by DC[2]
96 (1171)	87 (553)	–	–	–	–	Case (OV)-control study, FH taken by PI, verified by CR[4]
84 (39)[d]	–	–	–	–	–	Case (CHN) study, FH taken by PI, verified by MR[7]

Correct information: reported disease type (malignancy) and organ type both confirmed; n.r.: not reported. The first three studies determined accuracy of breast, colorectal and ovarian cancer for pooled first, second, and third-degree relatives, whereas the remainder did not include third-degree relatives. This fact alone could result in the lower rates found in the first three studies, compared with the others. In our study, accuracy for the three types of tumours in pooled first and second-degree relatives only, were 93% for breast cancer, 94% for colorectal cancer and 65% for ovarian cancer. We could not calculate this for the second and third studies, because the data needed were unavailable.
[a]first-degree relatives limited to parents; second-degree to grandparents; [b]first-degree relative or spouse; [c]mixed group of first and second-degree relatives; [d]first-degree relatives limited to sibs; FH: family history; PI: personal interview; MR: medical records; DC: death certificates; CR: cancer registry; GDB/CR: genealogic database linked to CR.
Codes referring to the type of proband in case (-control) studies: BR: breast cancer; CBT: childhood brain tumour; CHN: childhood head and neck condition treated with irradiation; COL: Colon cancer; ES: Ewing sarcoma; GLI: glioma; LW: lactating women; Mix: patients with a wide range of malignancies; OV: ovarian cancer; S: soft-tissue and bone sarcoma.
Not listed in this table is the study of 1040 reported melanomas in first-degree relatives of melanoma patients by Aitken *et al*[20] who obtained family history by mailed questionnaires and observed only 60% accuracy.

primary tumours, which are important for the interpretation of a family's history of cancer, were generally accurate in our study.

Because of its design, our study has two limitations. Firstly, the non-verified cases in our study might not be as accurate as the verified ones and thus the accuracy rates we found might not apply to all reported tumours in a family. This might mislead physicians in assessing family reports in cases where verification fails because of the absence of consent or, more importantly, because of the routine destruction of older medical records. We have, however, little reason to assume that accuracy in our non-verified cases is very different, because of the similarities between our findings and those observed in other studies which verified reports without the particular restrictions of our study (ie our need to obtain written consent from relatives and the blocked access to death certificates). The second limitation of our study is that we did not assess the accuracy of negative tumour reports. However, others have reported an accuracy of negative reports of 99% in their study on cancer in first-degree relatives.[15] We therefore expect little under-reporting of cancer in families referred for their family's history of cancer, since we expect those families to be alert to the occurrence of cancer. This may be especially true for close relatives, who are most important for genetic evaluation.

With respect to the impact of our verification effort, we note that most cancer-related referrals (approximately 90–95% in our clinic) are made because of familial clustering of breast or colorectal cancer and these tumour types are generally accurately reported. Therefore, it did not come as a surprise that the impact of verification on medical management turned out to be slight in our series.

Based on our findings and because of the need to increase efficiency, we have now significantly reduced the verification of reported breast cancer cases. Since referrals because of familial breast cancer are very frequent, this had a major impact on our overall verification. We do try, however, to verify the reports of breast cancer in our counsellees, because in our opinion documentation of our own patients should be complete before we counsel them. The effort to do this is relatively small, as most of the information is provided on referral to our clinic. In addition we also verify data on all relatives with breast cancer who participate in diagnostic DNA analysis and those breast cancer cases with notable clinical presentation (eg early-age at diagnosis, multiple primary tumours), because they strongly influence risk calculation,[16] interpretation of diagnostic DNA test results and planning of medical management.

One potential pitfall in our approach would be the referral of persons with a factitious breast cancer family history. Presumably, however, such an example of Münchhausen syndrome (by proxy) is very rare.[17,18] In general, in all cases where one has reason to suspect less than usual accuracy, eg when a counsellee was not in direct touch with any of the cancer patients in the family, or because of a counsellee's

particular psychiatric history, extra attention should be given to verification.

As a rule, we verify reported tumours other than breast cancer, unless they concern cancer in distant relatives (especially common late-onset types) where verification is expected to contribute little to the genetic diagnosis. Typical examples of histories which are left unverified are those of late-onset lung cancer in heavy smokers and late-onset non-melanoma cancer of skin exposed to the sun. Although family reports on colorectal tumours are generally accurate, we often verify them, because clinical and histological details usually unreported by the family may provide valuable information which helps to select tumour material as well as patients for DNA analysis. For a range of other tumour types (eg renal and thyroid cancer) verification of family histories remains the standard, as histological information may change radically the clinical genetic differential diagnosis.

Although the outcome of the different studies on the accuracy of family histories of cancer, including ours, shows may similarities (Table 3), it is conceivable that the nature of the population (mixed urban and non-urban in our case), which is served by a particular genetics centre, influences regional accuracy rates, and for this reason alone centres might want to conduct their own accuracy studies. Relevant differences between populations might, for example, exist in the strength of family ties, in the ways in which relatives share information on cancer and in the (national/regional) way physicians traditionally discuss disease details with their cancer patients.

If there are no organisational needs to limit verification, we recommend verifying the family medical history of at least first and second degree affected relatives, because in addition to the slight chance of clinical misinterpretation, another drawback of limited verification is that the value of pedigree information for research purposes may also be limited. In those cases where verification is impossible because medical records are unavailable, data from studies such as ours may help to evaluate the unverified family histories for clinical purposes. We expect, that the growing opportunity for DNA analysis will ultimately considerably lessen the need for full family history verification in the clinical setting, since diagnosing hereditary disorders by cheap and fast DNA analysis in a limited number of affected relatives will replace thorough verification and interpretation of extended family histories.

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