Original Article

Frequency of Colorectal Cancer and Extracolonic Tumors in Families That Meet Amsterdam Criteria I and II: Results From Hospital A. C. Camargo Hereditary Colorectal Cancer Registry (RHCC)

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Abstract

An estimated 1% to 10% of all colorectal tumors (CRC) are related to high-penetrance genes. Families with Lynch Syndrome, caused by mutations in MMR repair genes, present a high frequency, not only of CRC, but also extracolonic tumors. **Objective:** To verify the frequency of CRC and extracolonic cancers in families that meet Amsterdam I and II criteria. **Methods:** Families had been included that meet Amsterdam I and II criteria, in the Registry of Colorectal Cancer of A. C. Camargo Hospital from 1992 to 2007. Family history was taken and stored in the Cyrillic® 2.1 software. Data collection forms were filled. **Results**: 1578 individuals were identified, and 337 of them presented tumors. CRC was the most frequent, with 221 individuals, with a mean age of 46 years at diagnosis. The most frequent extracolonic tumors were breast (17 cases), endometrium (15), stomach (14), urinary (12), leukemia (9), and prostate (6). **Discussion:** As expected, the age at diagnosis of colorectal cancer was younger than the general population; breast tumor was the most frequent; molecular studies must differentiate patients with Lynch Syndrome (LS) from those with familial colorectal cancer.

Keywords: Colorectal Neoplasms. Hereditary Nonpolyposis Colorectal Neoplasms. Lynch Syndrome.

Introduction

Colorectal cancer (CRC) is one of the most common neoplasias in the world: in the year 2000 900,000 cases of the disease had been diagnosed, which represents 9.4% of all new cancer cases.[1]

Family history of CRC is one of the main risk factors for the development of cancer. De Jong and Vasen[2] in a population study with 5072 individuals of an rural region of Holland verified that 11.2% of individuals without cancer had reported at least one first-degree relative as having had colorectal cancer.

It is estimated that 1% to 10% of colorectal tumors are caused by high penetrance genes.The most common hereditary form of CRC is hereditary non-polyposis colorectal cancer (HNPCC), which, according to Lynch et al.[3] correspond to 2% to 7% of all CRC cases.

LS was described by Aldred Warthin in 1913, and its molecular base was initially elucidated by Peltomäki et al. in 1993, that identified a *locus* in the chromosome 2p.[3]

Recently a proposal was done for HNPCC to be called Lynch Syndrome. According to Lynch[4] naming the disease HNPCC can contribute to underdiagnosis, because the term "non-polyposis" can exclude families whose members present one or more adenomas. More-

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over, patients pertaining to families considered HNPCC not only present predisposition to colorectal cancer, but also to other tumors, such as endometrial, urinary tract, stomach or small bowel cancer, for example.

Amsterdam criteria continue valid as a clinical reference point in the characterization of Lynch Syndrome. However, there are individuals with tumors having microsatellite instability (MSI) and mutations in repair genes, but whose families do not meet Amsterdam criteria. On the other hand, 40% of families that meet such criteria do not present individuals having tumors with MSI, and do not present mutation in repair genes.[5]

Thus, LS can be defined in two ways: by meeting clinical criteria or by the presence of mutations of repair genes: *MSH2, MLH1, MHS6, PMS1* or *PMS2*.[6-8]

Lynch syndrome is characterized by the autosomal dominant inheritance pattern and the development of some tumors at younger age. LS has a broad spectrum of clinical manifestations including besides colorectal cancer, endometrial, stomach, small bowel, hepatobiliary tract, urologic tract, ovary and brain cancer. It is believed that prospective studies can broaden this spectrum.[7;9]

According to Lu and Broaddus[10] women with Lynch Syndrome have significant risks for endometrial cancer that can exceed the risks of colorectal cancer: from 25% to 64%. Also there is an increased risk for the development of ovarian cancer that can vary from 3% to 12%.

This study aims to describe the frequency of colorectal and extracolonic tumors in families that meet Amsterdam I and II criteria registered in the Hereditary Colorectal Cancer Registry (RHCC) of Hospital A. C. Camargo.

Methods

A retrospective and descriptive study was taken. The sample was constituted by families that meet Amsterdam I and II criteria registered in the RHCC of Hospital A. C. Camargo from 1992 to 2007.

Hospital A. C. Camargo's RHCC began its activities in 1992 and aims: identification of high-risk individuals for colorectal cancer; giving high-risk individuals instructions regarding strategies for risk reduction and early detection; and carry through research on hereditary cancer.[11]

In the RHCC, after the identification of patients diagnosed as having colorectal cancer in young age (below age 50) or with colorectal cancer and family history of cancer, the family history is taken adn stored in Cyrilic 2.1® software. The patient and family receive instructions regarding the risk of cancer and available of strategies for early detection.

Families that meet Amsterdam I and II criteria were included in this analysis. Amsterdam I criteria were defined by Vasen et al.:[12] three cases of colorectal cancer, one of the individuals must be a first-degree relative of the other two, at least two successive generations were affected, one of CRC must be diagnosed before age 50, and familial adenomatous polyposis must be excluded. Amsterdam II criteria, by their turn, consider besides CRC, tumors of the endometrium, small bowel, urinary tract for clinical diagnosis.[13]

From the information contained in the families' heredogram, clinical forms are filled with the following data: age, sex, tumor type, age at diagnostic and type of report (verbal or clinical/anatomopathological). Tumors of uncertain localization were excluded from the analysis.

Results are presented as relative and absolute frequencies and continuous variables are presented as mean.

Results

From the 250 registered families, 43 were classified as Lynch Sindrome: 36 (83.7%) Amsterdam I meet criteria and 7 (16.3%) meet Amsterdam II criteria.

In these 43 families, 1578 individuals were identified. The families presented an average 34.60 individuals (a minimum number of 4 and a maximum of 137), with an average of 8.21 affected individuals (considering polyps). From the total of 1,578 individuals, 789 were female (50%), 763 were men (48.4%) and on 26 individuals there were no information about sex.

From the total of 1.578 individuals 337 had tumors, but in 13 cases it was not possible to identify the location, so they were excluded from the analysis; 22 individuals had polyps. From the total of 1.578 individuals, 221 had colorectal cancer. From these 221 individuals, 209 had only 1 colorectal tumor, 10 had 2 colorectal tumors and 2 individuals had 3 colorectal tumors. The distribution of individuals according to tumor site and age at diagnosis is presented in Table 1.

Colorectal tumors with unknown localization correspond to proband's relatives not treated in the institution about which it was not possible to stablish the tumor localization in medical reports.

Table 2 presents the distribution of extracolonic tumors and the mean age at diagnosis.

Table 3 presents the individuals with diagnostic of multiple primary tumors and their age at diagnosis.

Table 1 - Distribution of individuals according to colorectal tumor site and age at diagnosis

Location	N	%	Mean age at diagnosis (yrs)
Right colon	21	9,5	46.24
Left colon	8	3.6	48.13
Rectum	21	9.5	40.28
Synchronic/metachronic tumor	12	5.4	41.70
Unknown	159	71.9	47.37
Total	221	100	46.01

Table 2 - Frequency of extracolonic tumors and mean age at diagnosis

Tumor location	N	%	Age at diagnosis (yrs)	
			Mean	Min-Max
Breast	17	14.7	50.83	31-84
Endometrium	15	12.9	48.86	31-74
Stomach	14	12.1	51	27-71
Urinary tract	12	10.3	48.75	35-70
Leukemia	9	7.8	31.75	3-55
Prostate	6	5.2	68.60	59-76
Esophagus	5	4.3	62.00	*
Ovary	5	4.3	45.75	27-59
Pancreas	4	3.4	67.67	60-74
Uterus no specified	4	3.4	49.50	45-54
Lung	3	2.6	58.00	49-67
Larynx	3	2.6	*	*
Cervix	3	2.6	44.00	37-51
Brain	3	2.6	32.50	17-48
Small bowell	2	1.7	43.10	41-46
Liver/billiary tract	2	1.7	*	*
Sebaceous adenocarcinoma	2	1.7	*	*
Melanoma	2	1.7	*	*
Lymphoma	2	1.7	40.00	21-59
Thyroid	1	0.9	28.00	*
Sarcoma	1	0.9	*	*
Vulva	1	0.9	41.00	*
Total	116	100	-	-

* no information available

From the 38 individuals with multiple primary tumors, CRC was the first tumor diagnosed in 28 cases. From the 38 individuals with multiple primary tumors, 11 had a colorectal tumor. In the individuals with CRC,

Table 3 - Individuals with multiple primary tumors (by order of diagnosis) and age at diagnosis

Family	Tumors (age at diagnosis - years)
001	CRC (37), Breast cancer (37)
002	Uterine cancer (37), CRC (49)
003	CRC (36), CRC (53)
	CRC (37), CRC (60)
004	CRC (29), CRC (32)
	CRC (44), Endometrial cancer (45), CRC (56)
005	CRC (42), Gastric adenomas (43), Small bowel cancer (44)
	CRC (61), Kidney cancer (61)
006	Breast cancer (54), Uterine cancer (54)
	CRC (unk), Prostate cancer (unk)
	Endometrial cancer (unk), Lymphoma (unk)
007	CRC (52), Melanoma (52)
008	CRC (71), Endometrial cancer (74)
009	CRC (48), Sebaceous carcinoma (48)
	CRC (unk), Gastric cancer (unk)
	CRC (unk), Endometrial cancer (unk)
010	CRC (47), Endometrial cancer (unk)
011	CRC (38), CRC (55)
	CRC (38), Uterine cancer (38)
012	CRC (25), Endometrial (31), Sebaceous carcinoma (31)
013	CRC (42), CRC (43)
	Small bowel carcinoma (41), ovarian cancer (59)
014	CRC (36), Endometrial cancer (36), CRC (49)
015	Endometrial cancer (49), Breast cancer (64), Pancreas (69)
	CRC (56), Prostate cancer (59), CRC (62)
016	CRC (67), Gastric cancer (67)
	Gastric cancer (63), CRC (63)
017	Prostate cancer (76), CRC (76)
018	CRC (43), Breast cancer (50)
019	CRC (49), Breast cancer (49)

CRC - colorectal cancer; unk - age unknown

endometrial cancer was the more frequent metachronic tumor (8 individuals). In 4 patients breast cancer and colon cancer were diagnosed. There were also in the individuals with multiple tumors, tumors not related to LS (melanoma, prostate cancer, uterine cancer and lymphoma).

Discussion

As expected colorectal tumors were the most frequent ones, with a high frequency of tumors located in the right colon, but there was also a high frequency of rectal tumors, similar to that observed by Goecke et al.[14] This fact must be considered when determining the surgical procedure in individuals with colon cancer and meeting Amsterdam criteria, since in these cases a total colectomy can be carried through.

The age at diagnosis of colorectal cancer was 46 years, compatible with the description of the syndrome.

Amongst extracolonic tumors, breast cancer was the most frequent; however, if we added together endometrial tumors and cervical tumors without specification, endometrial tumors would be most frequent. We opted for this division because in four individuals it was not possible to detect whether the tumor was endometrial or cervical. Since cervical tumors are frequent in Brazilian population, it is not possible to establish the accurate localization of these tumors.

In most tumors considered associated to Lynch Syndrome (stomach, small bowel, endometrium, ovary and urinary tract), the mean age at diagnostic was less than the observed in sporadic cases, and compatible with the syndrome description. Stomach tumor is considered part of LS, but it is not part of Amsterdam II criteria. In our sample it was one of the most frequent extracolonic tumors. A high prevalence of gastric cancer was observed in other studies, specially the ones carried through with the Asiatic population.[15;16]

In our sample we identified two small bowel tumors: one diagnosed in a woman with ovary tumor and the other in an individual with CRC and gastric adenomas. Small bowel tumors are rare and respond to less than 2% of gastrointestinal tumors, but in individuals with LS the risk for tumors of the small bowel is from 1% to 4%, 100 times higher than in the general population. In a collaborative study, Park et al.[17] identified 87 patients with cancer of the small bowel in 78 families with mutation in repair genes. Data were gotten from questionnaires sent to 13 countries.

From the 43 families that meet Amsterdam I and II criteria, 14 presented cases of breast cancer, and four individuals presented colon and breast cancer at the same time. These 14 families, besides meeting LS clinical criteria, also present clinical criteria for Breast-Colon Syndrome. The association between breast cancer and colon cancer was described by Lynch in the decade of 1970.[11] Meijers-Heijboer al. ,[18] considering the existence of the association between breast cancer and colon cancer, carried through a study to verify the frequency of mutation in gene *CHEK2* in a group of families with cases of breast cancer associated to colorectal cancer: from the 55 families who meet clinical criterion for Hereditary Breast-Colon Syndrome, 10 (18.2%) presented mutation in *CHEK2*. Naseem et al.,[19] by their turn, investigating 113 families who meet criteria for Hereditary Breast-Colon Syndrome, Lynch Syndrome or Breast-Ovary Syndrome, found only one mutation *CHEK2* 1100delC; 14 families presented mutation in *BRCA1* or *BRCA2* and seven presented mutations in repair genes (*MLH1, MSH2*). In our study, 6.5% of families with mutations in *MSH2* meet clinical criteria for Breast-Colon Syndrome.

Amongst the 333 individuals with cancer, two individuals with sebaceous adenocarcinomas were identified: one with colorectal cancer and another with colorectal and endometrial tumors. The clinical criterion for diagnosis of Muir-Torre Syndrome is the occurrence of a sebaceous neoplasia (adenomas, epitheliomas, carcinomas) and an internal malignancy (regardless family history). CRC is the most frequent neoplasia and the tumor spectrum is similar to that of LS, and since there were identified mutations in MMR genes, Muir-Torre Syndrome is considered a phenotypic variant of LS.[11]

One must consider that information gathered on family history considered verbal reports and evidences from medical reports. There were difficulties in confirming cases of neoplasia by means of anatomopathological reports. This can be attributed to the following factors: absence of a health system without reference and counter-reference, families with a high number of individuals and inhabiting in distant cities, the fact that cancer is not a disease of mandatory notification. It must be pointed out, however, that the accuracy of the information on family history of cancer had already been evaluated. Ziogas and Anton-Culver[20] evaluated 1,111 families and verified that the agreement between the report and the occurrence of cancer in first-degree relatives was 95.4% for breast cancer, 89.7% for CRC, 83.3% for ovary cancer and 79.3% for prostate cancer. Reports of cancer without the proven presence of the disease were rare, occurring in only 2.4% of cases.

One must point out that this analysis only involved

clinical data, without molecular analysis. Lindor et al.[21] consider that the term Lynch Syndrome is used only for families with identified mutations in repair genes. For families that meet Amsterdam I and II criteria, but without identification of mutations in repair genes they proposed the designation of families with family colorectal cancer. Molecular analysis of these families is in progress, with sequencing of genes *hMHL1, hMSH2, hMSH6, PMS2* and *CHEK2*. With these data a more accurate characterization of families with LS will be possible.

Conclusion

From the total of 1,578 individuals pertaining to 43 families that meet Amsterdam I and II criteria 337 tumors were observed: 221 presented colorectal cancer, with mean age at diagnosis of 46 years. The most frequent extracolonic tumors were: breast (17 cases); endometrium (15); stomach (14); urinary tract (12); leukemia (9) and prostate (6).

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