Artigo de revisão

Neoplasias primárias múltiplas: uma revisão

Multiple primary cancers: an overview

Autores:
Filipa Macedo
Filipa Pinho
Nadine Saraiva
Nuno Bonito
Luísa Pinto
Francisco Gonçalves

Afiliação:
Filipa Macedo
Portuguese Oncology Institute of Coimbra
Filipa Pinho
Braga Hospital
Nadine Saraiva
Portuguese Oncology Institute of Coimbra
Nuno Bonito
Portuguese Oncology Institute of Coimbra
Luísa Pinto
Braga Hospital
Francisco Gonçalves
Braga Hospital

Conflitos de interesse:
Sem conflitos de interesse.

Financiamento:
Não se aplica.

Autor para correspondência:
Filipa Castro Macedo
Av. Bissaya Barreto 98, 3000-075
Email: filipa.c.macedo@gmail.com
Tel: +351 916842232

Resumo

A prevalência de doentes que vivem após o diagnóstico de cancro tem vindo a aumentar devido ao aumento da sua incidência, melhoria dos tratamentos e aumento da sobrevivência. O risco de neoplasias primárias subsequentes deve ser esperado devido ao efeito dos factores de risco comportamentais e genéticos, efeitos adversos das terapias, aumento da sensibilidade de diagnóstico e envelhecimento. A prevalência de neoplasias primárias múltiplas situa-se entre 0,7 e 11,7% e os doentes com um cancro tem um risco 20% maior comparativamente com a população geral. Mama, coloretal e próstata são os locais de maior prevalência de tumores múltiplos devido à sua elevada incidência e sobrevivência global.

Com este artigo pretendemos rever o tema das neoplasias múltiplas e sumarizar as mais frequentes síndromes que levam a neoplasias múltiplas.

Palavras-chave: neoplasias primárias múltiplas, síndromes hereditários associados a cancro, cancro da mama, cancro coloretal

Abstract

The prevalence of patients living after a diagnosis of cancer has increased due to the rising incidence, better treatments and improved survival rate. The risk of further primary cancers might be expected to be rising because of the persisting effects of genetic and behavioural risk factors, long-term side-effects of chemo and radiotherapy, increased diagnostic sensitivity, and aging. The prevalence of multiple primary cancers is between 0.7% and 11.7%, and cancer patients have a 20% higher risk of new primary cancer compared with the general population. Breast, colon-rectum, and prostate are the sites with highest prevalence of multiple tumours since these tumours have higher incidence and longer survival.

In this paper we review the theme of multiple tumours and summarise the most frequent cancer syndromes that lead to multiple tumours.

Keywords: *multiple primary neoplasms, hereditary cancer syndromes, breast cancer, colorectal cancer*

Introduction

Multiple primary tumours are a major cause of mortality and morbidity amongst patients that have survived after the treatment of a first cancer.[1] Advances in early detection, treatment and supportive care have led to a record number of cancer survivors or individuals living with cancer.[2] Cancer survivors amount to more than 3% of the population in Western Europe.[3]

Multiple primary cancers comprise two or more primary histologically distinct malignancies occurring in the same individual, which originate in a primary site or tissue and are neither an extension, nor a recurrence or metastasis.[4] They were firstly described by Billroth in 1889 and later described by Warren and Gates in 1932.[5]

Multiple primary cancers generally fall into two categories: synchronous, in which the cancers occur at the same time (within 6 months), and metachronous, in which the cancers follow in sequence more than 6 months apart).[6,7] If a patient has a cancer diagnosis at an early stage and a subsequent cancer is detected, it is more likely to be a second primary than a recurrence. Some literature consider the time limit for this type of diagnosis as 2 months instead of 6 months.[6,7]

Risk factors for the development of multiple primary cancers: genetic predisposition to cancer; the usual carcinogenic or cancer-promoting aspects of lifestyle, hormonal and environmental factors; treatment of the previous primary cancer (iatrogenic risks associated with chemotherapy, radiotherapy and hormonal therapy); increased surveillance of cancer survivors; and ageing.[1,2,4,8] When a person is genetically predisposed to develop cancer, it will happen earlier in life than a person who develops cancer sporadically.[6] The mechanisms involved in the occurrence of multiple primary malignancies are not yet elucidated; however, microsatellite instability (MSI) was observed to occur more frequently in cases of multiple primary cancers than in sporadic cancers.[9-11] Some alterations are necessary for both the establishment and the maintenance of the oncogenic state; therefore, they are logical drug targets.[12] They are the gain-of-function mutation; the amplification or overexpression of an oncogene; the loss-of-function mutation; the deletion or epigenetic silencing of a tumour suppressor gene and the non-oncogenes.[12] The subset of oncogenes whose inhibition can lead to tumour cell death, differentiation, arrest or senescence are of great clinical interest as targets for cancer therapeutics, such as imatinib and Philadelphia chromosome (BCR-ABL), erlotinib and epidermal growth factor receptor (EGFR), trastuzumab and human epidermal growth factor receptor (HER2), bevacizumab and vascular endothelial growth factor (VEGF).[13] Targeting non-kinase oncogenes, such as RAS and MYC, has proven more difficult. Tumour suppressor genes act to provide the cellular restraints necessary to prevent aberrant growth and survival, or genomic instability.[12] The loss of tumour suppressor genes results in the removal of these restraints leading to tumorigenesis.[12] Finally, the tumorigenic state depends on the activities of a wide variety of genes and pathways, many of which are not inherently oncogenic themselves.[14] These are essential to support the oncogenic phenotype of cancer cells but are not required to the same degree for the viability of normal cells.[14] Non-oncogene genes fall into two categories, tumour intrinsic (e.g. DNA damage, mitotic stress or hypoxia), and tumour extrinsic (e.g. angiogenesis or stromal support).[12] All these alterations are usually somatic events, although germline mutations can predispose a person to heritable or familial cancer.[15]

Regarding second tumours due to chemotherapy, the main agents responsible for new diseases are: a) alkylating agents, leading to acute myeloid leukaemia at 1–2 years after the start of chemotherapy and peaking 5–10 years after treatment; b) topoisomerase II inhibitors, responsible for leukaemia, M4 and M5 subtypes involving monocytes; and c) anthracyclines, when given in a high dose, increase the risk of developing leukaemia, non-Hodgkin lymphoma and epidermal cancers.[16]

Methods

The authors reviewed the theme of multiple tumours and summarised the most frequent cancer syndromes that lead to them. A PubMed search was made ("multiple primary neoplasms" [All Fields]), focusing on reviews written in English during the last 10 years. A total of 446 articles were obtained. Exclusion criteria were articles related to metastatisation, haematology, no relation to multiple cancers, no relation to cancer, and rare cancers not related to syndromes. Finally, a revision of the bibliography of the main articles was performed.

Epidemiology

Cancer patients have a 20% higher risk of new primary cancer compared with the general population.[4] Approximately one-third of cancer survivors aged > 60 years were diagnosed more than once with another cancer.[4] In the Surveillance, Epidemiology and End Results (SEER) study, 10% of patients, from a total of 2.7 million cancers, developed a second cancer. Of the individuals who had multiple primaries, 20% were synchronous and 80% were metachronous. Overall, approximately 10% of patients had more than one cancer.[8]

The prevalence of multiple primary cancers is estimated to be between 0.7% and 11.7%.[17] Even a study performed in 1966 revealed that 3.7% of cancers were discovered simultaneously in the same host.[18] From the cancer survivors diagnosed with more than one primary malignant tumour, 74% had two or more cancers of different primary sites, whereas 26% were from the same site.[2] In autopsies, 3.1% occult second primary cancers were revealed in different organs or tissues.[7] Additionally, clinically apparent second primary cancers in different organs or tissues were observed at an average annual incidence rate of 10.9 per 1,000.[7]

Localisations

Urinary bladder is the initial primary cancer site with the highest percentage of individuals with multiple primary cancers, followed by oropharynx and corpus/uterus. Liver cancer has the fewest multiple primary occurrences.[8] A risk factor for hepatocellular carcinoma shared with other types of cancer is primary biliary cirrhosis.[19]

Breast, colon-rectum and prostate are the sites with the highest prevalence of multiple tumors.[2] This is expected because the proportion of multiple tumours is higher for those cancers with high incidence and long survival.[20] The female breast

is the site with the highest percentage of individuals with more than one primary of the same site.[2] Among males, the most frequent site for a second or later primary is the prostate followed by the colon and rectum.[2] For females, the most frequent second or later sites are breast, the female genital system and the colon and rectum.[2] For both male and female survivors, there is a higher frequency of having later tumours of the same sites as the first tumour, as well as tumours in the most frequent sites of cancer, such as the prostate in men and the breast in women.[2] Cancers of the same site occur more frequently within 5 years of the original diagnosis, and the most likely time for a second or later tumour of a different site to occur is between 5 and 10 years from the diagnosis of the primary tumor.[2] As expected, there is an association between the risk of developing subsequent cancers and patient survival.[8]

Urinary bladder cancer patients have an elevated risk of subsequent cancers of the kidney and other urinary organs.[8] Oropharynx cancer patients have an increased risk for cancer of the esophagus.[8] Some risk factors for oral cavity cancer are shared with other types of cancer, such as tobacco, alcohol and human papillomavirus (HPV).[21] HPV has been identified in approximately 23.5% of oral cavity cancer cases.[22] The most commonly detected HPV in head and neck squamous cell carcinoma is HPV-16, followed by HPV-18, HPV-31 and HPV-33.[21] The prognostic significance of HPV in pre-cancerous oral lesions is not clear.[21]

Kidney and renal pelvis cancer patients have an elevated risk of multiple primary cancers at the same or proximal site, as well as in the bladder.[8] Colon and rectum cancer patients have a significant risk of subsequent cancer of the colon.[8] For a first cancer of the corpus and uterus, the risk of multiple primaries of the bladder and other urinary organ diseases is elevated.[8] In breast cancer cases, a significantly increased risk for subsequent cancer of the corpus uteri was observed and interpreted as the common shared risk factors, such as low parity, early menarche and late onset of menopause.[3]

Interestingly, patients with multiple malignancies demonstrated improved 5-year survival compared to patients with corresponding solitary malignancies.[10] It is unclear whether these patients have some manner of increased tumour resistance or if these survival rates were simply necessary for the development of multiple cancers in the first place.[10]

Breast cancer

As far as breast cancer is concerned, patients can have synchronous multiple primaries (multicentric cancer of the same breast or synchronous contralateral breast cancer) and metachronous contralateral or ipsilateral tumors.[6] The decision regarding primary treatment must be made if these are ipsilateral recurrences or new primaries.[6] Generally, contralateral breast cancers are new primaries; they are not metastases.[6] The incidence of contralateral breast cancer is approximately 8% among patients who do not have inherited susceptibility to breast cancer (the inherited susceptibility risk of developing contralateral breast cancer may be as high as 40–50% by age 70).[6] For female breast cancer, the risk of contralateral breast cancer is 3% after 5 years.[23]

Patients undergoing breast-conserving surgery are just as likely to develop an ipsilateral breast cancer as they are a contralateral breast cancer.[24] Clinicians consider cancers to be a recurrence when they arise in the same quadrant of the breast or the same site as the primary.[24] One study defined new primaries as different histologies or different locations in the breast, and recurrences as the same histologies or the same locations in the breast.[24] The increased risk of a subsequent cancer located in the anatomical sites of the oesophagus, stomach, lung or thyroid is suggestive of a late effect of local radiotherapy of the breast tumor.[24]

The breast cancer susceptibility genes 1/2 (*BRCA1/2*) are tumour suppressor genes involved in pathways important for controlling DNA damage.[25] The mechanisms by which *BRCA1/2* mutations lead to cancer of the breast and ovaries are not fully understood; however, *BRCA1* and *BRCA2* mutations increase breast and ovarian cancer risks substantially enough to warrant risk reduction surgery.[25] In addition to breast and ovarian cancer in women, and breast and prostate cancer in men, *BRCA1* and *BRCA2* carriers may be at higher risk for additional malignancies, such as gastric cancer.[26] The risk for gastric cancer is reported to be 4-fold greater in *BRCA1* mutation carriers and at least 2-fold greater in *BRCA2* mutation carriers.[27] There is little information about the nature and frequency of *BRCA2* constitutional mutations in families selected for the coexistence of breast and stomach cancers.[28] Male breast cancer and prostate cancer are higher in *BRCA2* compared to *BRCA1* carriers.[26] Concerning penetrance, the cumulative risks by age 70 years are 55% for breast cancer in *BRCA1* and 47% for *BRCA2* mutation, and 39% for ovarian cancer for *BCRA1* and 17% for *BRCA2* mutation carriers.[29] Mutations in exon 2 of the *BRCA1* gene had significantly lower penetrance compared with mutations of exons 11, 13 and 20. The median age for the diagnosis of breast cancer was 55 years for the exon 2 mutation, 47 years for exon 11 and 41 years for exon 13.[30] All of these patients had an indication to perform risk-reducing bilateral mastectomy and salpingo-oophorectomy[31] (Table 1).

Colorectal cancer

The incidence of multiple primary cancers identified in the colon and rectum is approximately 2–5%.[32] This incidence increases to 10–20% in patients with familiar adenomatous polyposis, hereditary non-polyposis, colorectal cancer and ulcerative colitis.[32]

The rates reported for metachronous colon tumours range from 0.5% to 9% and for synchronous colon tumours from 2% to 10%, depending on the methodological approach and length of follow-up.[33] Stage distribution of the synchronous colorectal cancers and second tumours of metachronous cancers is better than that of single tumors.[29,30] The time intervals between the diagnosis of index and metachronous cancers varied obviously, and they can range from 8 months to 20 years.[34]

Finan et al.[35] reported that synchronous colorectal cancers were missed in 58% of patients at pre-evaluation (24% were identified by intra-operative evaluation and 34% were identified in post-operative specimen). The identification of tumours in the proximal colon by colonoscopy can be limited by obstruction of lesions in the distal colon.[36] In these cases, intra-operative palpation or intra-operative colonoscopy are essential.[36] The identification of two cancers is mandatory to decide the surgical approach, since synchronic colon cancer can be managed with one extensive resection or with two separate resections.[37] A total colectomy could be necessary if both the right and left sides of the colon are affected.[37]

Important mutations identified in colorectal cancer are: a) Mutations in the *BRAF* gene, an oncogenic kinase, are found in about 10% of patients.[38] These mutations are associated with shorter progression-free survival and overall survival.[38] b) Mutations in *KRAS*, an oncogene that encodes a binding protein of the EGFR pathway, are found in 35–45% of colorectal cancers.[39] Mutations are negative predictors of response to anti-EGFR antibodies (cetuximab and panitumumab).[39] c) Mutations in *PTEN*, a tumour suppressor gene involved in the homeostatic maintenance of PI3K/*Akt* signalling from EGFR activation.[40] *PTEN* expression and mutational rate was reported to be lower in left-sided (distal) colon cancer compared to right-sided (proximal) cancers.[40] The role of *PTEN* as a prognostic factor is controversial.[40] d) Mutations in PIK3CA, the catalytic subunit of PI3K, have been reported in 10–20% of colon cancer.[41] In RAS wild-type colon cancer, PIK3CA mutations have been associated with a worse clinical outcome and with a negative prediction of a response to targeted therapy by anti-EGFR monoclonal antibodies.[41] e) MSI is due to an abnormal DNA mismatch repair, which is unable to correct errors that occur during DNA replication.[42] This creates novel microsatellite fragments. Colon cancers due to MSI are predominantly formed in the proximal colon, have a better prognosis and are hereditary. However MSI is present in 13% of sporadic colon cancer cases.[42]

Cancer syndromes

Many families have at least a few members who have had cancer.[43] In these cases, the cancer is caused by an abnormal gene that is being passed along from generation to generation.[43] Only about 5–10% of all cancers result from an abnormal gene (mutation) inherited from a parent (inherited cancer).[43]

An inherited cancer susceptibility is suspected in families with the following characteristics: two or more relatives with the same type of cancer on the same side of the family; several generations affected; earlier ages of cancer diagnosis than what is typically seen for that cancer type; individuals with multiple primary cancers; the occurrence of cancers in one family, which are known to be genetically related (such as breast and ovarian cancer); and the occurrence of non-malignant conditions and cancer in the same person and/or family (e.g. Marfanoid habitus and medullary thyroid cancer in multiple endocrine neoplasia type 2B).[44]

Cancers derived from inherited gene mutations tend to occur earlier in life than cancers from acquiring mutations, because acquiring two mutations in the same gene takes longer than acquiring one.[43]

Some examples of family cancer syndromes are: (Table 1)

1. **Hereditary breast and ovarian cancer syndrome:** these cancers were found at younger ages and some of the women had more than one cancer (some had breast cancer in both breasts and some had both breast and ovarian cancer).[44,45] The responsible genes are *BRCA1*, *BRCA2* and *BRCA3* (this last gene has not yet been identified but is attributed when women have the syndrome based on cancer history but do not have mutations in *BRCA 1* or *2*).[44,45] This syndrome can also lead to fallopian tube cancer, primary peritoneal cancer, gastric cancer, male breast cancer pancreatic cancer and prostate cancer.[44,45] The risk of breast and ovarian cancer tends to be higher with *BRCA1* mutations.[44,45] Male breast cancer, pancreatic cancer and prostate cancer are more common with *BRCA2* mutations.[44,45]
2. **Hereditary non-polyposis colorectal cancer** (HNPCC) or **Lynch syndrome:** this syndrome leads to an increased risk of colorectal cancer. HNPCC also leads to a high risk of endometrial cancer and is linked to cancer of the ovary, stomach, small intestine, pancreas, brain, ureters and bile duct.[45] HNPCC can be caused by mutations in several genes, including *MLH1, MSH2, MLH3, MSH6, PMS1, PMS* and *TGFBR2* (most are involved in DNA repair).[45] Males with HNPCC have virtually a 100% chance of developing colorectal cancer by age 70.[45] Women appear to have a higher lifetime risk of endometrial cancer (42–60%) than colorectal cancer (54%).[45,46] In both men and women whose first tumour is not treated with subtotal colectomy, the risk of developing a second primary colorectal cancer is 30% within 10 years after the original surgery, and 50% within 15 years.[45] Women with HNPCC have a 9–12% lifetime risk of developing ovarian cancer.[26] The distinctive characteristics of HNPCC compared with sporadic colorectal cancer are: the average age of onset is approximately 45 years (63 years in the general population); there is poverty of adenomatous colonic polyps; the proximal colon is the preferred site (60–70%) and there is significant risk for synchronous and metachronous cancers; the progress from adenoma to carcinoma occurs more rapidly (2–3 years); these tumours are often poorly differentiated; and these lesions are associated with a better prognosis than sporadic colon tumors.[44]
3. **Familial adenomatous polyposis** (FAP): this accounts for approximately 1% of hereditary colorectal cancer.[44] FAP is characterised by the development of hundreds to thousands of adenomatous polyps throughout the colon and rectum, with an extremely high lifetime risk of colon cancer.[44] It is caused by germline mutations in the *APC* gene.[44] The clinical diagnosis of FAP is made if an individual has more than 100 colorectal adenomas.[44] The average age of colorectal cancer diagnosis is 39 years.[45] Historically, the

presence of both colonic and extracolonic features has been referred to as Gardner syndrome.[46,47] Individuals with FAP can develop extracolonic malignancies: gastric adenomas and fundic gland polyps are common but the associated risk for cancer is small; the adenomas that form in the second and third portions of the duodenum represent an increased risk (4–12%) for malignancy; papillary thyroid carcinoma occurs in approximately 2% of individuals with FAP (most often in females); and other cancers include hepatoblastoma in children, pancreatic carcinoma and central nervous system tumors.[44]

4. **Li-Fraumeni syndrome:** this is a rare syndrome associated to sarcoma, leukaemia, brain cancers, cancer of the adrenal cortex and breast cancer.[44] The cancers most often occur in childhood, and people affected with this syndrome can have more than one cancer in their lifetime.[44] They also seem to be at higher risk of cancer from radiotherapy.[44] This syndrome is caused by inherited mutations in the *p53* gene, which is a tumour suppressor gene. (When normal, *p53* induces the apoptosis of abnormal cells.)[44]
5. **Multiple endocrine neoplasia type 1** (MEN1): the major endocrine features of MEN1 are parathyroid adenomas, entero-pancreatic endocrine tumours, and pituitary tumors.[45] The diagnosis of MEN1 is made in a person with two of the three major endocrine tumors.[45] Familial MEN1 is defined as at least one MEN1 case plus at least one first-degree relative with one of these three tumors.[45] It is caused by germline mutations in the *MEN1* gene (it acts like a tumour suppressor gene).[45] Primary hyperparathyroidism is the most common, occurring in 80–100% of patients by the age of 50. Pancreatic islet cell tumours, usually gastrinomas and insulinomas, and less commonly VIPomas (vasoactive intestinal peptide), glucagonomas and somatostatinomas, are the second most common endocrine manifestation, occurring in 30–80% of patients by the age of 40.[44] Non-functional tumours of the entero-pancreas, some of which produce pancreatic polypeptide, are seen in 20% of patients. Approximately 15–50% of MEN1 patients will develop a pituitary tumor.[44]
6. **Multiple endocrine neoplasia type 2** (MEN2): this is characterised by medullary thyroid cancer, phaeochromocytoma, and/or primary hyperparathyroidism.[45] MEN2 has been divided into three subtypes depending on the clinical features: MEN2A, MEN2B and familial medullary thyroid carcinoma.[45] MEN2A classically comprises medullary thyroid cancer in 100% of affected individuals, phaeochromocytoma in 50% and primary hyperparathyroidism in 15–30%.[44] In MEN2B the average age of tumour onset is 10 years younger than MEN2A; primary hyperparathyroidism is not clinically manifest, and other features, such as marfanoid habitus and mucosal neuromatosis, are present.[44] Familial medullary thyroid carcinoma is defined as the presence of medullary thyroid cancer in the absence of phaeochromocytoma and primary hyperparathyroidism.[44] MEN2 are caused by germline mutations of the RET proto-oncogene.[44]

Table 1. Principle cancer syndromes.

Syndrome	Gene	Incidence	Cancer	Suspicion criteria	Screening
Hereditary breast and ovarian cancer syndrome	*BRCA 1* *BRCA 2*	1/300–800 (Ashkenazi:1/40)	Breast, ovary, melanoma, prostate, pancreatic, gastric	- Breast cancer <50 years - Male breast cancer - Ovarian cancer - Two primary breast cancers - Triple negative breast cancer < 60 years - Combination of pancreatic cancer and/or prostate cancer with breast cancer, and/or ovarian cancer - Breast cancer diagnosed at any age in an individual of Ashkenazi Jewish ancestry - Two or more relatives with breast cancer, one under age 50 - Three or more relatives with breast cancer at any age - A previously identified *BRCA1* or *BRCA2* pathogenic variant in the family	Annual breast MRI and/or mammogram starting between the ages of 25 and 29 years old.

Table 1. ***Continuation.***

Syndrome	Gene	Incidence	Cancer	Suspicion criteria	Screening
Lynch syndrome	*MLH1* *MSH2* *MSH6* *PMS2* *EPCAM*	1/660–2000	Uterine, colon, ovary, pancreatic, gastric, small intestine, CNS, renal, sebaceous	Revised Bethesda Criteria: - CRC diagnosed at < 50 years - Synchronous or metachronous CRC or other Lynch syndrome-associated tumours - CRC with MSI-high pathologic-associated features diagnosed at < 60 years old - CRC or Lynch syndrome-associated tumours diagnosed in at least one first-degree relative < 50 years old - CRC or Lynch syndrome-associated tumours at any age in two first-degree or second-degree relatives Amsterdam Criteria: - ≥ 3 family members, one of whom is a first-degree relative of the other two, with a confirmed diagnosis of CRC - Two affected generations - > 1 CRC diagnosed before age 50 years Amsterdam II Criteria: - ≥ 3 family members (one of whom is a first-degree relative of the other 2) with HNPCC-related cancers - Two affected generations - > 1 HNPCC-related cancers diagnosed before age 50 years	Annual colonoscopy beginning at the age of 25 years old or 5–10 years before the earliest case in the family.
Familial adenomatous polyposis	*APC*	1/10,000	Colon/rectum, gastrointestinal, papillary thyroid cancers	- 0–99 adenomatous colon polyps, or >100 polyps diagnosed at an older age than that expected for FAP (age 35–40 or older)	Annual colonoscopy in patients and first-degree relatives at the age of 12–14 years. Annual upper endoscopy and neck ultrasonography starting at the age of 25–30 years.
Li-Fraumeni syndrome	*P53*	Unknown	Breast, sarcomas, uterine, thyroid, colon, renal	- A proband with a sarcoma diagnosed before age 45 years AND - A first-degree relative with any cancer before age 45 years AND - A first- or second-degree relative with any cancer before age 45 years or a sarcoma at any age	Annual mammography (+ MRI) starting at 25–30 years old Consider whole-body MRI.

Table 1. ***Continuation.***

Syndrome	Gene	Incidence	Cancer	Suspicion criteria	Screening
MEN1	*MEN1*	2/100,000	Primary hyper-parathyroidism, pancreatic islet-cell tumours, anterior pituitary tumours	- Two or more primary MEN1 tumour types, - Family members of a patient with a clinical diagnosis of MEN1, the occurrence of one of the MEN1-associated tumours	Calcium, PTH and prolactin dosing, 24-hr urinary metanephros, renin and aldosterone starting at 10 years old. Neck ultrasonography if calcium elevated. 2-yearly MRI abdomen. 2-yearly non-contrast MRI pituitary. Low dose CT chest at age 18 or at time of diagnosis.
MEN2	*RET*	1/35,000	Medullary thyroid carcinomas, (MTC), pheochromocyto-mas, mucosal neuromas	- Distinctive facies including lip mucosal neuromas resulting in thick vermilion of the upper and lower lip, mucosal neuromas of the lips and tongue, medullated corneal nerve fibres, marfanoid habitus - A patient with a personal/ family history of MTC - A patient with a personal/ family history of phaeochromocytoma - Infants or young children with Hirschsprung disease - Patients with cutaneous lichen amyloidosis	Yearly blood tests for ionised calcium and parathyroid hormone levels, beginning in childhood. Yearly blood tests for catecholamines and catecholamine metabolites (metamachine and normetanephrine), beginning in childhood. MRI or CT of the abdomen to detect pheochromocyto-mas, every 4 to 5 years or when abnormal catecho-lamine or meta-machine levels are detected.

Table 1. ***Continuation.***

Syndrome	Gene	Incidence	Cancer	Suspicion criteria	Screening
Von Hippel-Lindau (VHL)	*VHL*	1/36,000	Renal-cell carcinomas, retinal and CNS hemangioblastomas, pheochromocytomas	- Retinal angioma, especially in a young individual - Spinal or cerebellar hemangioblastoma - Adrenal or extra-adrenal pheochromocytoma - Renal cell carcinoma, if the individual is younger than age 47 years or has a personal or family history of any other tumour typical of VHL - Multiple renal and pancreatic cysts - Neuroendocrine tumours of the pancreas - Endolymphatic sac tumours - Multiple papillary cystadenomas of the epididymis or broad ligament	Annual paediatric examinations and ophthalmoscopy until the age of 5 years. From 5 to 14 years, annual plasma-metamachine and plasma-normetanephrine tests + annual hearing examinations. MRI of the CNS and abdomen between the ages of 8 and 14 years. After the age of 15 years, individuals should be referred to: annual ophthalmoscopy in dilation; annual neurological examination; every 2 years: MRIs of the CNS, including the inner ear; annual ultrasound/MRI of the abdomen; annual plasma-metamachine, plasma-normetanephrine, and plasma-chromogranin A tests; and annual hearing examination at a Department of Audiology.

Adapted from Orphanet.

CNS – central nervous system; CRC – colorectal cancer; CT – computed tomography; FAP: familial adenomatous polyposis; HNPCC – hereditary non-polyposis colorectal cancer; MEN – multiple endocrine neoplasia; MRI – magnetic resonance imaging; MSI – microsatellite instability; MTC – medullary thyroid carcinomas; PTH – parathyroid hormone; VHL – Von Hippel-Lindau.

Conclusion

Given that cancer is a disease associated with aging, as the population ages and cancer survival lengthens, the growing number of survivors with multiple malignant primary tumours will become an increasingly important medical issue, particularly among the elderly.

Studies on multiple primary cancers have several challenges; for example: rigorous cancer registry information and differential diagnosis (which will permit the separation of initial primary cancers from subsequent new primaries from metastases and from recurrences); the availability of medical record information because occasionally the clinical processes are destroyed; the need for a large population base, which some-times requires the participation of multiple centres; a long-term registry because it takes time for multiple cancers to occur; patients lost to follow-up because they've moved to another geographic area; and the time it takes to perform the studies.

Information regarding multiple primaries is important to clinicians and cancer patients during medical management following initial treatment, and in the efforts to minimise the iatrogenic effects of cancer therapy identified through analyses of multiple primaries.

The possibility that multiple primary cancers exist must always be considered during pretreatment evaluation. Screening procedures are especially useful for the early detection of associated tumours, preferably before clinical manifestations occur. The early diagnosis of secondary malignancies should not be neglected in patients treated for a primary malignancy.

Good communication between patients and doctors is essential; doctors should give warnings regarding the risk of developing secondary malignancies after the primary treatment and patients should advise the doctors of the occurrence of any new symptoms.

There are no accepted clinical counselling guidelines or action plans for familial cancer at large. Familial clustering of cancer has been one of the main avenues to the understanding of cancer aetiology and the signal of the involvement of heritable genes. Recently, the introduction of next-generation sequencing technology in testing for hereditary cancer susceptibility has allowed the testing of multiple cancer susceptibility genes simultaneously.[48]

Genetic counsellors are an essential part of the cancer risk assessment team, helping the medical team select the most appropriate test and interpret the often complex results. Genetic counsellors obtain an extended family history; counsel patients on the available tests and the potential implications of results for themselves and their family members; explain to patients the implications of the test results; and assist in testing family members at risk.

Todos os autores com nome neste trabalho cumprem os critérios estabelecidos pela International Committee of Medical Journal Editors (ICMJE), assumindo toda a responsabilidade pela integridade de todo o trabalho e aprovação final da versão a ser publicada.

All authors named in this study meet the criteria established by the International Committee of Medical Journal Editors (ICMJE), assuming full responsibility for the integrity of the work and final approval of the version to be published.

References

1. Canto L, Basso T, Villacis R, Giacomazzi J, Ashton-Prolla P, Waddington M. Genomic alterations in patients showing multiple primary tumours and family history of cancer. Ann Oncol. 2014;25(4):165-166.
2. Mariotto A, Rowland J, Ries L, Scoppa S, Feuer E. Multiple cancer prevalence: a growing challenge in long-term survivorship. Cancer Epidemiol Biomarkers Prev. 2007;16(3): 566-571.
3. Rosso S, Terracini L, Ricceri F, Zanetti R. Multiple primary tumours: incidence estimation in the presence of competing risks. Popul Health Metr. 2009;7:5.
4. Soerjomataram I, Coebergh J. Epidemiology of multiple primary cancers. Methods Mol Biol. 2009;471:85-105.
5. Warren S, Gates O. Multiple primary malignant tumours: a survey of the literature and a statistical study. Am J Cancer. 1932;16:1358-1414.
6. Howe H, editor. A Review of the Definition for Multiple Primary Cancers in the United States. North American Association of Central Cancer Registries (New Jersey); 2002.
7. Schottenfeld D. The epidemiology of multiple primary cancers. CA Cancer J Clin. 1977;27(4):233-240.
8. Hayat M, Howlader N, Reichman M, Edwards B. Cancer statistics, trends, and multiple primary cancer analyses from the surveillance, epidemiology, and end results (SEER) program. Oncologist. 2007;12:20–37.
9. Irimie A, Cadariu P, Burz C, Puscas E. Multiple Primary Malignancies – Epidemiological Analysis at a Single Tertiary Institution. J Gastrointestin Liver Dis. 2010;19(1):69-73.
10. Williamson C, Paravati A, Ghassemi M, et al. Five simultaneous primary tumours in a single patient: a case report and review of the literature. Case Rep Oncol. 2015;8:432-438.
11. Horii A, Han HJ, Shimada M, et al. Frequent replication errors at microsatellite loci in tumours of patients with multiple primary cancers. Cancer Res. 1994;54:3373-3375.
12. Luo J, Solimini N, Elledge S. Principles of cancer therapy: oncogene and non-oncogene addiction. Cell. 2009; 136(5):823-837.
13. Weinstein IB. Cancer. Addiction to oncogenes-the Achilles heel of cancer. Science. 2002;297:63-64.
14. Solimini NL, Luo J, Elledge SJ. Non-oncogene addiction and the stress phenotype of cancer cells. Cell. 2007;130:986-988.
15. Croce C. Oncogenes and cancer. N Engl J Med. 2008;358: 502-511.
16. Vega-Stromberg T. Chemotherapy-induced secondary malignancies. J Infus Nurs. 2003;26(6):353-361.

17. Demandante CG, Troyer DA, Miles TP. Multiple primary malignant neoplasms: case report and a comprehensive review of the literature. Am J Clin Oncol. 2003;26:79-83.

18. Spratt J, Hoag M. Incidence of multiple primary cancers per man-year of follow up: 20-year review from the Ellis Fischel State Cancer Hospital. Ann Surg. 1966;164:775-784.

19. Sanyal A, Yoon S, Lencioni R. The etiology of hepatocellular carcinoma and consequences for treatment. Oncologist. 2010;15(4):14-22.

20. Rosso S, Angelis R, Ciccolallo L, et al. Multiple tumours in survival estimates. Eur J Cancer. 2009;45(6):1080-1094.

21. Ram H, Sarkar J, Kumar H, Konwar R, Bhatt M, Mohammad S. Oral Cancer: Risk Factors and Molecular Pathogenesis. J. Maxillofac. Oral Surg. 2011;10(2):132-137.

22. Kreimer A, Clifford G, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev. 2005;14(2):467-475.

23. Gao X, Fisher S, Emami B. Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: a population-based study. Int J Radiat Oncol Biol Phys. 2003;56:1038-1045.

24. Smith T, Lee D, Turner B, Carter D, Haffty B. True recurrence vs. new primary ipsilateral breast tumor relapse: an analysis of clinical and pathologic differences and their implications in natural history, prognoses, and therapeutic management. Int J Rad Oncol Biol Phys. 2002;48(5):1281-1289.

25. Gudmundsdottir K, Ashworth A. The roles of BRCA1 and BRCA2 and associated proteins in the maintenance of genomic stability. Oncogene. 2006;25:5864-5874.

26. Levy-Lahad E, Friedman E. Cancer risks among BRCA1 and BRCA2 mutation carriers. Br J Cancer. 2007;96:11-15.

27. Cavanagh H, Rogers K. The role of BRCA1 and BRCA2 mutations in prostate, pancreatic and stomach cancers. Hered Cancer Clin Pract. 2015;13(1):16.

28. Jakubowska A, Nej K, Huzarski T, Scott R, Lubinski J. BRCA2 gene mutations in families with aggregations of breast and stomach cancers. Br J Cancer. 2002;87:888-891.

29. Chen S, Parmigiani G. Meta-Analysis of BRCA1 and BRCA2 Penetrance. J Clin Oncol. 2007;25(11):1329-1333.

30. Al-Mulla F, Bland J, Serratt D, Miller J, Chu C, Taylor G. Age--dependent penetrance of different germline mutations in the BRCA1 gene. J Clin Pathol. 2009;62(4):350-356.

31. Mau C, Untch M. Prophylactic surgery: for whom, when and how. Breast Care. 2017;12:379-384.

32. Yoon J, Lee S, Ahn B, Baek S. Clinical characteristics of multiple primary colorectal cancers. Cancer Res Treat. 2008;40(2):71-74.

33. Rennert G, Robinson E, Rennert H, Neugut A. Clinical characteristics of metachronous colorectal tumours. Int J Cancer. 1995;60(6):743-747.

34. Papadopoulos V, Michalopoulos A, Basdanis G, et al. Synchronous and metachronous colorectal carcinoma. Tech Coloproctol. 2004;8:97-100.

35. Finan P, Ritchie J, Hawley P. Synchronous and 'early' metachronous carcinoma of the colon and rectum. Br J Surg. 1987;74:945-947.

36. Barillari P, Ramacciato G, De Angelis P, et al. Effect of preoperative colonoscopy on the incidence of synchronous and metachronous neoplasms. Acta Chir Scand. 1990;156: 163-166.

37. Mekenkamp L, Koopman M, Teerenstra S, et al. Clinicopathological features and outcome in advanced colorectal cancer patients with synchronous vs metachronous metastases. Br J Cancer. 2010;103:159.

38. Barras D. BRAF mutation in colorectal cancer: an update. Biomark Cancer. 2015;7(1):9-12.

39. Tan C, Du X. KRAS mutation testing in metastatic colorectal cancer. World J Gastroenterol. 2012;18(37):5171-5180.

40. Molinari F, Frattini M. Functions and regulation of the PTEN gene in colorectal cancer. Front Oncol. 2013;3:326.

41. Cathomas G. PIK3CA in colorectal cancer. Front Oncol. 2014;4:35.

42. Boland C, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology. 2010;138(6):2073-2087.e3.

43. Berger AH, Pandolfi PP. Cancer susceptibility syndromes. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology. 8th ed. 2011; 161-172. Wolters Kluwer Health / Lippincott Williams & Wilkins.

44. Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. Oncogene. 2000;23:6445-6470.

45. Lindor N, McMaster M, Lindor C, Greene M. The Concise Handbook of Family Cancer Syndromes – second edition. J Nat Cancer Inst Monogr. 2008;38:1-93.

46. Aarnio M, Sankila R, Pukkala E, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer. 1998;81:214-218.

47. Gardner E, Richards R. Multiple cutaneous and subcutaneous lesions occurring simultaneously with hereditary polyposis and osteomatosis. Am J Hum Genet. 1953;5: 139-147.

48. Stanislaw C, Xue Y, Wilcox W. Genetic evaluation and testing for hereditary forms of cancer in the era of next-generation sequencing. Cancer Biol Med. 2016;13(1):55-67.