SUMMATIVE REPORT
ON SITUATION/STRATEGIES/SUPPORT INSTITUTIONS AND SPECIALISTS/BEST PRACTICES OF THE GENETIC CONSULTANCY/ ONCOGENETICS IN ROMANIA, FRANCE, BULGARIA AND HUNNGARY

Report created in the framework of the project Promoters of advanced oncogenetics open online training and multimedia raise awareness on multidisciplinary assessment of patients and their families at risk of hereditary or familial cancer, Reference number 2018-1-RO01-KA202-049189, Strategic Partnerships for vocational education and training Erasmus+ programme

1. Current epidemiological situation of cancer, and of hereditary cancer in particular (breast, ovarian, colorectal and other types).

1.1. Incidence

FRANCE

In 2012, the number of cancers diagnosed in metropolitan France is estimated at 355,354 for the population over 15 years, with respectively 200,350 men and 155,004 women (1). With 56,840 new cases estimated in 2012, prostate cancer remains by far the most common cancer in men, with lung cancer (28,200 cases) and colorectal cancer (23,200 cases). With 48,800 new cases estimated in 2012, breast cancer is the most common cancer in women, with colorectal cancer (18,920 cases) and lung cancer (11,300 cases). The median age at diagnosis of any cancer is estimated at 68 years for men and 67 years for women. For breast cancer in women, the median age at diagnosis was 63 years, while for colorectal cancer it was 71 years in men and 75 years in women. Ovarian cancer is the 7th leading cause of cancer in women, with an incidence of 4,615 cases. He is diagnosed most frequently after 65 years.

The incidence of pediatric cancers (<15 years) was between 1,700 and 2,500 new cases of cancer per year between 2006 and 2010. The main localizations are leukemia (29% of cases), tumors of the central nervous system (24%) and lymphomas (11%) (1).

Between 5 and 10% of breast and ovarian cancers are secondary to hereditary predisposition (HBOC). BRCA1 and BRCA2 are the principal genes involved. 2,500 to 5,000 new HBOC cases are diagnosed each year, with approximately 21,000 cases diagnosed between 2003 and 2014 (2). Other hereditary predisposition syndromes are less frequent.

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Approximately 5% of colorectal cancer cases are genetically predisposed, representing 2,000 new cases per year. Other cancers, such as paraganglioma-pheochromocytoma or medullary thyroid carcinoma, are also associated with inherited predisposition.

The following data used in this summative report are available from International Agency for Research on Cancer (IARC) – GLOBOCAN 2018.

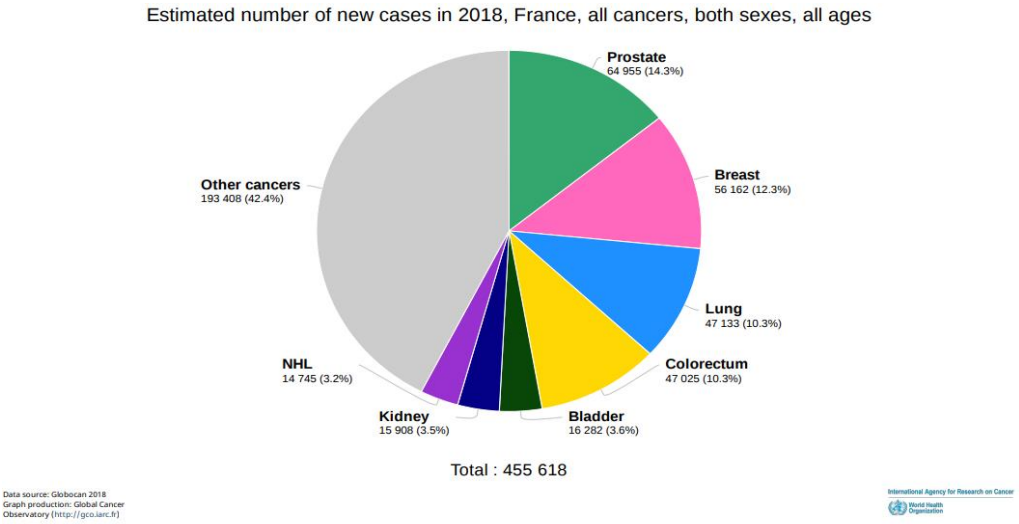

Fig. 1 Estimated number of new cases of cancer, France, 2018

ROMANIA

Analysing the estimated incidence values for the main categories of cancers developed by Romanian women in 2008, one can see a change in 2nd and 3th positions, the colorectal neoplasia climbed one step in hierarchy, and the cervical cancer recorded a slight decline. For 5th and 6th positions, ovarian cancer increased (although as numerical values, the situation has not significantly changed), and the gastric cancer decreased. (Fig. 2) **[GLOBOCAN 2008]**

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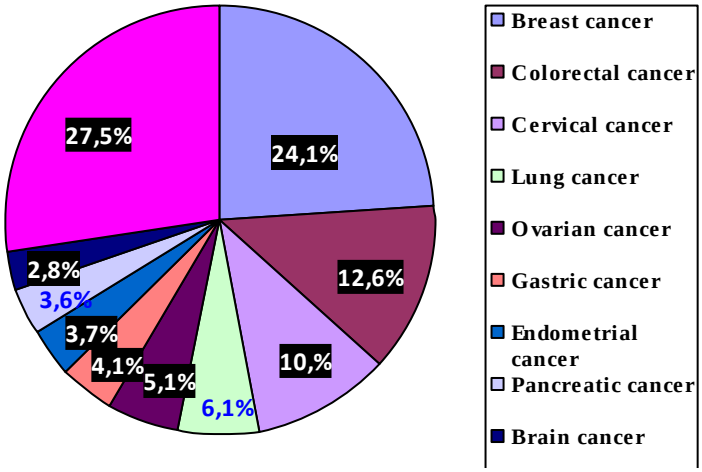

Fig. 2. Incidence (standardized by age) for the main types of cancers developed by women, in Romania, 2008

In 2008, among women in the North-East Region of Romania, ovarian cancer had an incidence of 12.17 / 100.000 women (the 6th position) and a frequency of 5.02% of all female cancers. In the same year, in Iasi County, ovarian cancer had the 5th place (with 12,17 cases per 100,000 women), after breast cancer (50,11 cases per 100,000 women), colorectal (33,4 cases in 100,000 women), cervical (25.05 cases in 100.000 women) and lung cancer (18.37 cases per 100.000 women). According to the same source, the incidence of ovarian cancer in Iasi County in 2008 was 12,17 cases per 100,000 inhabitants, placing this county on the 4th place when we compare the incidence of ovarian cancer among the counties of the North-East region of Romania (Table I) **[Gheorghiu, 2011]**.

Table I

The incidence of ovarian cancer in counties within the North-East Region of Romania, in 2008

Nr.crt	**County**	**Number of new cases of ovarian cancer**	**Female population at 1 July 2008**	**Incidence (per 100.000 inhabitants)**
1.	Suceava	49	357,220	13.71
2.	Botosani	31	229,260	13.52
3.	Neamt	36	286,173	12.57
4.	Iasi	51	419,113	12.17
5.	Vaslui	27	226,689	11.91
6.	Bacau	35	362,822	9.64
	North-East Region	229	1,881,277	12.17

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Regarding to age, the same report states that the most affected women in the North-East Region of Romania were those in the 55-59 age group (17.03% of the new ovarian cancer), 75-79 years (13,10%), 70-74 years (11,35%) and 65-69 years (10,04%). 68% of the cases were diagnosed among women aged over 55 years **[Gheorghiu, 2011]**.

In 2008, in Romania, ovarian cancer was ranked 5th among women's neoplasms with an incidence value (standardized by age) of 9.4 cases / 100,000 women.

According to the International Agency for Research on Cancer (IARC), in Romania, in 2018, the estimated total number of new cases of cancer for both sexes at all ages was 83,461 (GLOBOCAN 2018). Case distribution by location indicates that lung cancer was the most common (13.6%), followed by colorectal cancer (13.3%), breast cancer (11.5%), prostate cancer (7.2%), bladder cancer (4.7%), gastric cancer (4.2%), liver cancer (4.1%) and other cancers (41.3%) (Fig. 3). Among the other cancers that were recorded we mention: uterine cancer (2.9%) and ovarian cancer (1.6%) **[GLOBOCAN 2018]**.

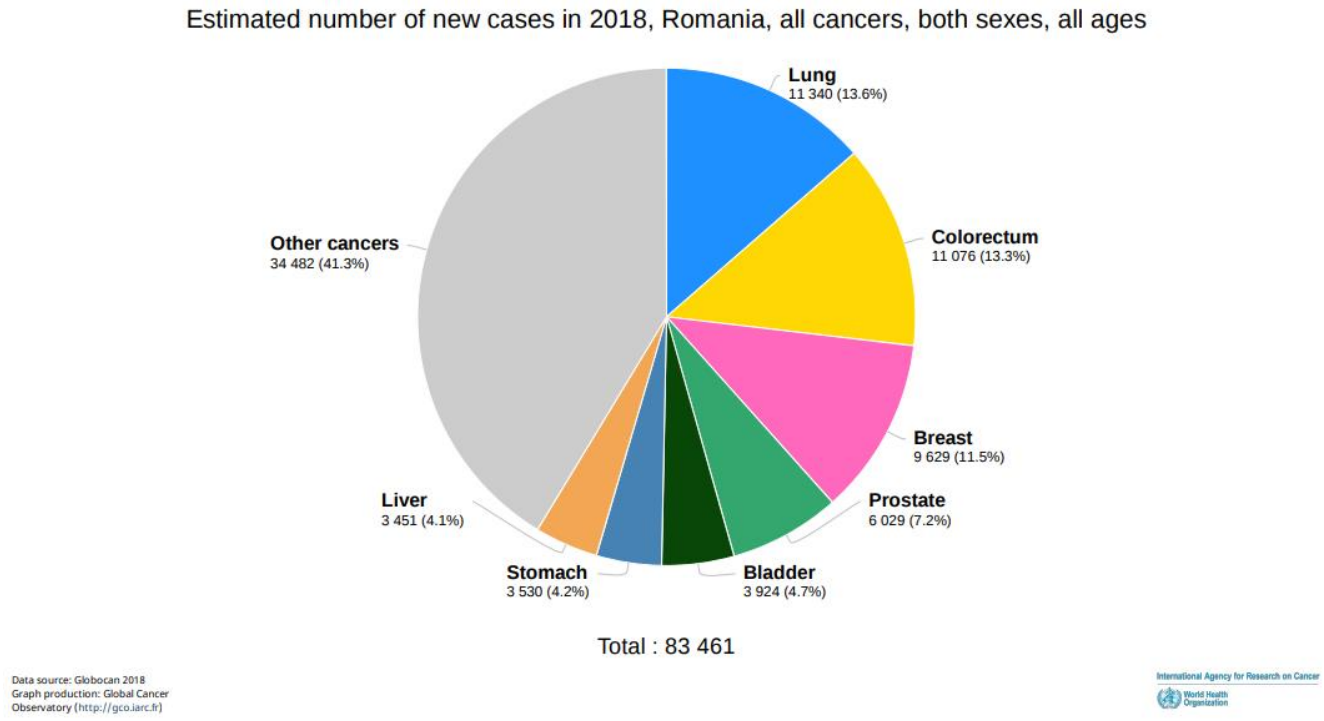

Fig. 3. The estimated number of new cases of cancer, both sexes, all ages, in Romania

(*Source*: *** International Agency for Research on Cancer. GLOBOCAN 2018. *Globocan cancer observatory*. Available from: http://gco.iarc.fr.)

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Comparing these data with those published by Straja ND et al. in 2015 one can observe the upward trend in the number of new cases for all types of cancer. For breast cancer, the number of new cases has risen from 8,981 estimated for both sexes in 2012 to 9,629 in 2018. Colorectal cancer has evolved from 10,256 new cases in 2012 to 11,076 in 2018. Uterine cancer has varied from 1,539 new cases in 2012 to 1,635 in 2018 and ovarian from 1,850 new cases in 2012 to 1,920 in 2018 (Table II) **[GLOBOCAN 2018; Straja et al, 2015]**.

Table II

Variation of new cases of breast, colorectal, ovarian and uterine cancer in Romania, 2018 versus 2012 (adapted from **[GLOBOCAN 2018; Straja et al, 2015]**)

Types of cancer	Years	TOTAL		WOMEN		MEN	
		No.	%	No.	%	No.	%
Breast	2018	9,629	11.5	9,629	11.5	-	-
	2012	8,981	11.40	8,981	25.22	-	-
Colorectal	2018	11,076	13.3	5,020	11.51	6,056	12.13
	2012	10,256	13.02	4,496	12.63	5,760	13.35
Ovarian	2018	1,920	1.61	1,920	3.44	-	-
	2012	1,850	2.35	1,850	5.20	-	-
Uterine	2018	1,635	2.87	1,635	6.13	-	-
	2012	1,539	1.95	1,539	4.32	-	-

HUNGARY

CANCER TODAY enables a comprehensive assessment of the cancer burden worldwide in 2018, based on the GLOBOCAN estimates of incidence, mortality and prevalence for year 2018 in 185 countries or territories for 36 cancer types by sex and age group **[http://gco.iarc.fr/today/home]**.

Hungary

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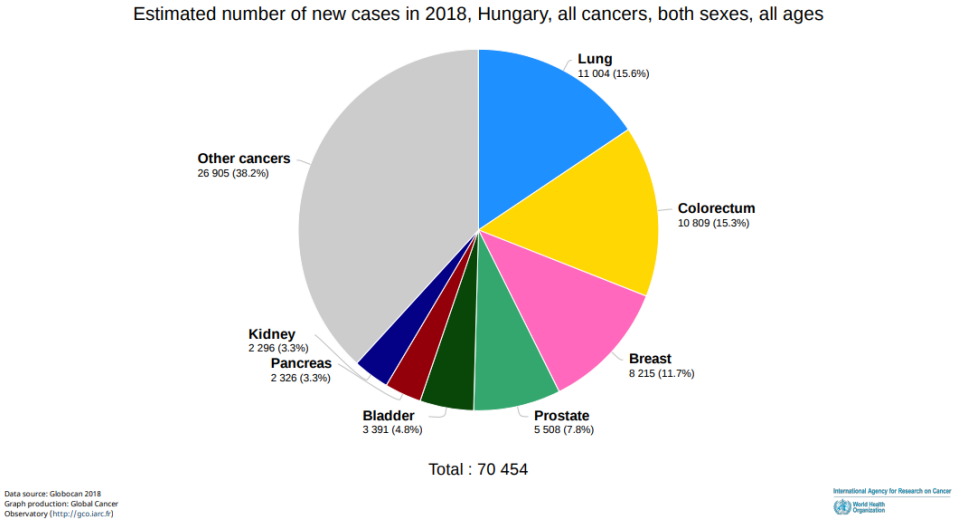

Fig. 4. The estimated number of new cases of cancer, both sexes, all ages, in Hungary (*Source*: *** International Agency for Research on Cancer. GLOBOCAN 2018. *Globocan cancer observatory*. Available from: http://gco.iarc.fr.)

Summary statistic 2018			
	Males	**Females**	**Both sexes**
Population	4 610 879	5 077 967	9 688 846
Number of new cancer cases	35 281	35 173	70 454
Age-standardized incidence rate (World)	427.1	330.6	368.1
Risk of developing cancer before the age of 75 years (%)	63.4	49.2	54.9
Number of cancer deaths	17 586	15 424	33 010
Age-standardized mortality rate (World)	203.2	122.0	155.8
Risk of dying from cancer before the age of 75 years (%)	42.9	27.7	33.6
5-year prevalent cases	85 345	99 932	185 277
Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases)	Lung Colorectum Prostate Bladder Kidney	Breast Colorectum Lung Corpus uteri Cervix uteri	Lung Colorectum Breast Prostate Bladder

Fig. 5 Summary statistic 2018 [*Source:* *** International Agency for Research on Cancer. GLOBOCAN 2018. *Globocan cancer observatory*. Available from: http://gco.iarc.fr.]

Table III
Estimated number of new cases in 2018, Hungary, females, all ages

ICD	Cancer	Number	Uncertainty interval	Crude Rate*	ASR (World)*	Cum. risk**
C00-97	**All cancers**	35 173	[34435.1-35926.7]	692.7	330.6	-
C50	Breast	8 215	[7518.2-8976.4]	161.8	85.5	-
C18-21	Colorectum	4 694	Not available	92.4	36.8	-
C33-34	Lung	4 537	[4278.6-4811.0]	89.3	41.4	-
C54	Corpus uteri	1 919	[1625.9-2264.9]	37.8	18.2	-
C53	Cervix uteri	1 312	[1124.5-1530.8]	25.8	17.2	-

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ICD	Cancer	Number	Uncertainty interval	Crude Rate*	ASR (World)*	Cum. risk**
C56	Ovary	1 305	[1153.0-1477.0]	25.7	13.2	-
C25	Pancreas	1 233	[1116.8-1361.3]	24.3	9.1	-
C67	Bladder	1 057	[873.7-1278.8]	20.8	9.1	-
C73	Thyroid	999	[731.4-1364.6]	19.7	13.6	-
C64-65	Kidney	991	[819.8-1197.9]	19.5	8.8	-
C43	Melanoma of skin	944	[739.1-1205.7]	18.6	10.1	-
C16	Stomach	861	[751.2-986.9]	17.0	6.3	-
C82-86, C96	Non-Hodgkin lymphoma	809	[634.3-1031.9]	15.9	7.4	-
C91-95	Leukaemia	686	[573.3-820.8]	13.5	7.2	-
C23-24	Gallbladder	477	[405.8-560.6]	9.4	3.2	-
C00-06	Lip, oral cavity	417	[295.7-588.0]	8.2	3.8	-
C70-72	Brain, nervous system	406	[323.7-509.2]	8.0	4.7	-
C22	Liver	317	[248.3-404.8]	6.2	2.4	-
C51	Vulva	251	[177.4-355.1]	4.9	2.0	-
C88+C90	Multiple myeloma	219	[163.3-293.7]	4.3	1.8	-
C09-10	Oropharynx	216	[160.5-290.7]	4.3	2.4	-
C32	Larynx	177	[117.8-266.0]	3.5	2.0	-
C15	Oesophagus	118	[79.2-175.8]	2.3	1.1	-
C81	Hodgkin lymphoma	93	[48.9-177.0]	1.8	1.9	-
C07-08	Salivary glands	87	[51.6-146.6]	1.7	1.00	-
C52	Vagina	68	[43.3-106.7]	1.3	0.55	-
C12-13	Hypopharynx	55	[37.0-81.8]	1.1	0.58	-
C11	Nasopharynx	39	[22.0-69.2]	0.77	0.47	-
C45	Mesothelioma	19	[10.1-35.7]	0.37	0.17	-
C46	Kaposi sarcoma	3	[1.4-6.4]	0.06	0.01	-

*** Crude and age-standardized rates per 100 000**

Table IV
Estimated number of new cases in 2018, Hungary, males, all ages

ICD	Cancer	Number	Uncertainty interval	Crude Rate*	ASR (World)*	Cum. risk**
C00-97	**All cancers**	35 281	[34594.4-35981.2]	765.2	427.1	-
C33-34	Lung	6 467	[6158.1-6791.4]	140.3	77.4	-
C18-21	Colorectum	6 115	Not available	132.6	70.6	-
C61	Prostate	5 508	[5021.9-6041.1]	119.5	60.2	-
C67	Bladder	2 334	[1990.3-2737.0]	50.6	26.9	-
C64-65	Kidney	1 305	[1096.3-1553.4]	28.3	16.6	-
C16	Stomach	1 228	[1072.9-1405.5]	26.6	13.8	-
C25	Pancreas	1 093	[956.7-1248.7]	23.7	12.9	-
C32	Larynx	922	[788.0-1078.7]	20.0	12.0	-
C00-06	Lip, oral cavity	893	[739.8-1077.9]	19.4	11.8	-
C43	Melanoma of skin	780	[576.6-1055.2]	16.9	10.3	-
C82-86, C96	Non-Hodgkin lymphoma	774	[642.5-932.4]	16.8	10.4	-

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ICD	Cancer	Number	Uncertainty interval	Crude Rate*	ASR (World)*	Cum. risk**
C22	Liver	770	[665.5-890.9]	16.7	9.2	-
C91-95	Leukaemia	765	[648.5-902.4]	16.6	10.6	-
C15	Oesophagus	628	[509.8-773.6]	13.6	8.1	-
C62	Testis	554	[377.8-812.5]	12.0	10.7	-
C09-10	Oropharynx	518	[410.3-654.0]	11.2	7.3	-
C12-13	Hypopharynx	471	[391.8-566.3]	10.2	6.5	-
C70-72	Brain, nervous system	434	[354.0-532.1]	9.4	6.6	-
C23-24	Gallbladder	279	[222.3-350.1]	6.1	3.0	-
C88+C90	Multiple myeloma	230	[172.5-306.6]	5.0	2.7	-
C73	Thyroid	192	[120.9-305.0]	4.2	3.0	-
C81	Hodgkin lymphoma	128	[75.1-218.2]	2.8	2.7	-
C60	Penis	113	[72.5-176.0]	2.5	1.3	-
C07-08	Salivary glands	78	[51.4-118.3]	1.7	0.98	-
C11	Nasopharynx	69	[47.2-100.9]	1.5	0.98	-
C45	Mesothelioma	28	[17.0-46.1]	0.61	0.36	-
C46	Kaposi sarcoma	7	[2.7-18.3]	0.15	0.06	-

*** Crude and age-standardized rates per 100 000**

BULGARIA

It is observe the upward statistically significant trend in the number of new cancer cases for all types. Over the past 20 years, the number of newly registered cancer cases has risen by an average of 678.81 cases per year (Fig. 6).

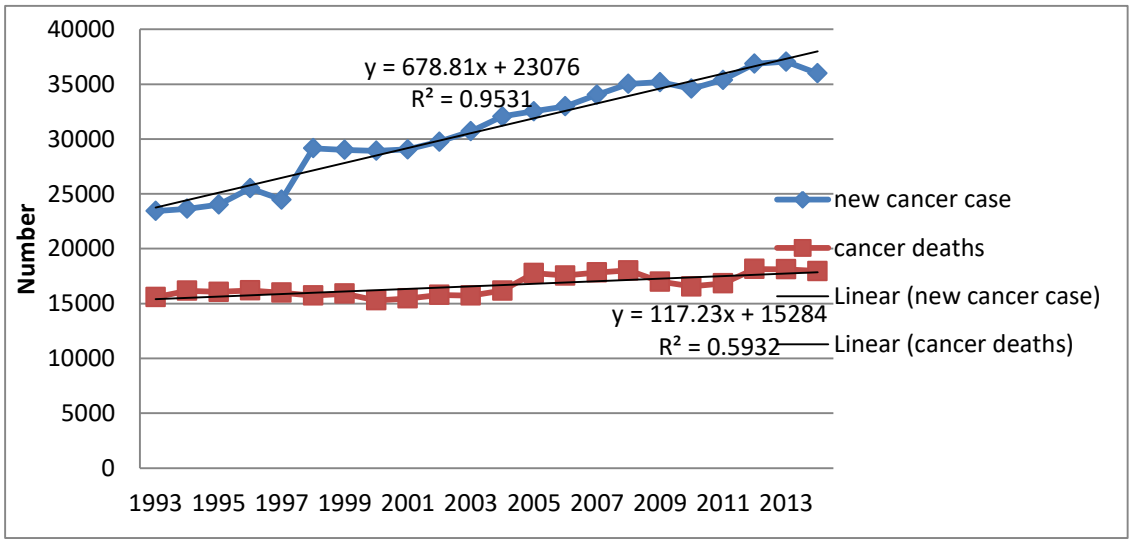

Fig.6. Number of new cancer cases and deaths in Bulgaria (1993-2014)

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According to BNCR data for cancer incidence in Bulgaria in 2015, the number of new cancer cases were 35265 and the crude incidence rate was 491.3 per 100 000 inhabitants. In men the prevalence was higher - 530/100 000, whereas in women it was 454.7/100 000 inhabitants.

The newly diagnosed breast cancer cases in females were 3988 with a crude incidence rate of 108.1 per 100 000; for ovarian cancer - 825 new cases with a crude incidence rate of 22.4/100000.

In colon cancer the crude incidence rate in males was higher as compared to that of females - 1541 cases, or 44.2/100 000 *vs* 1202 cases, or 32.6/100 000, respectively. The total crude incidence rate for colon cancer in Bulgaria was 38.2/100 000 for year 2015.

Breast cancer is the most common malignant disease among women. It represents 26.8 % of all malignant diseases in females. Colon cancer comes third in incidence (8.1%), ovarian cancer is fifth (5.5%). Colon cancer is third in incidence in males as well (9.5%) (Fig. 7).

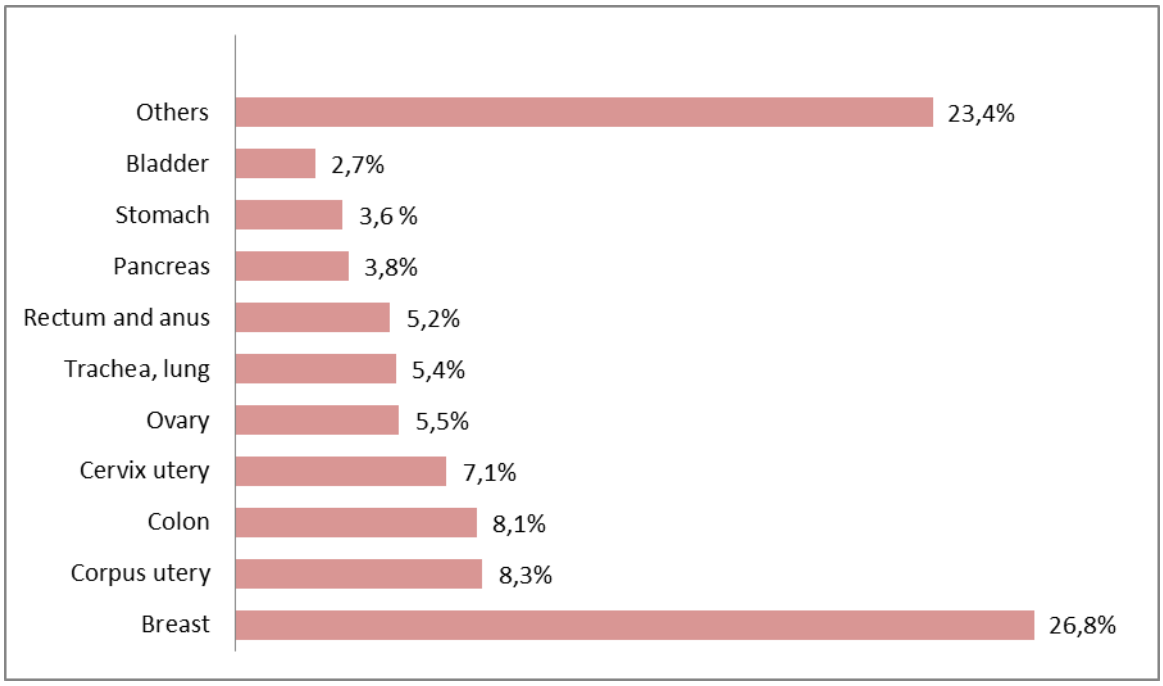

Fig.7. Percentage distribution of the most common cancers in females in Bulgaria, 2015

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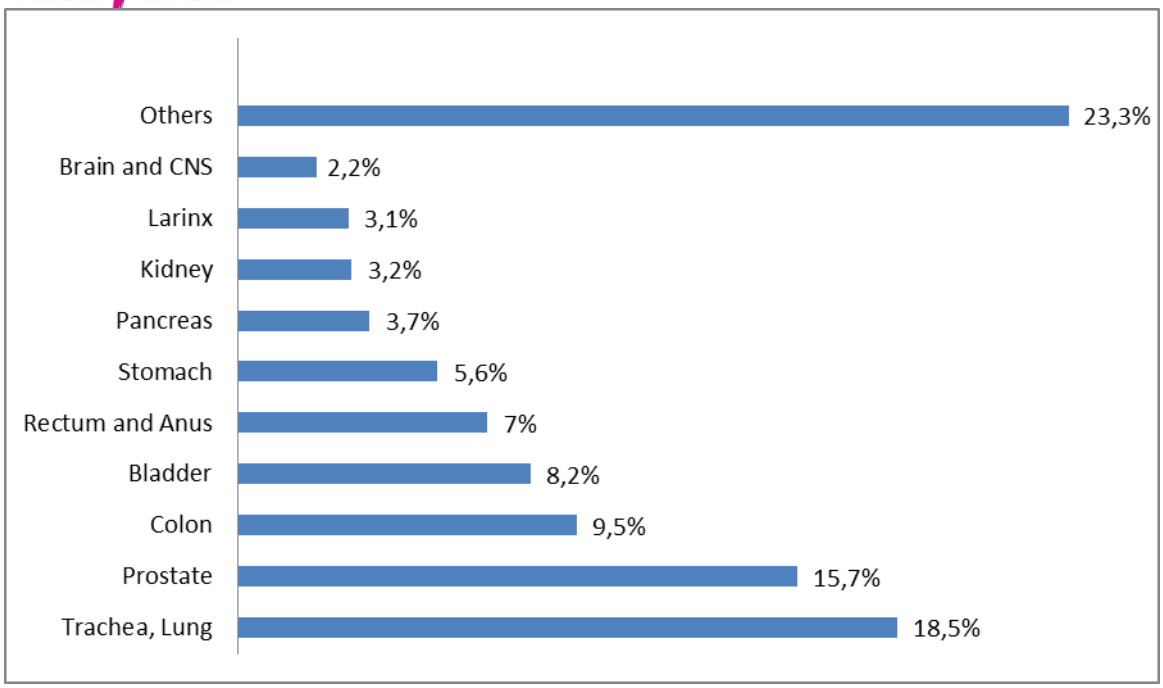

Fig.8. Percentage distribution of the most common cancers in males in Bulgaria, 2015

Disturbing is the fact that a great part of the newly diagnosed cases were in an advanced stage. The distribution of the incidence of breast, ovarian and colon cancer by stage at diagnosis is presented in Fig.9.

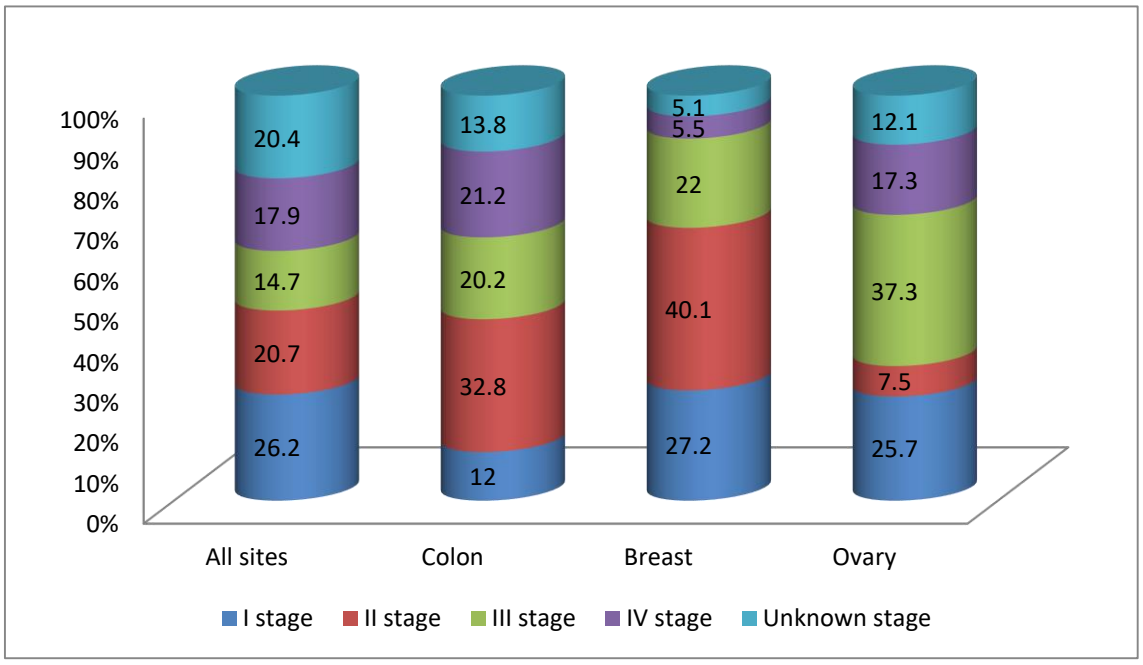

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Fig.9. Distribution of the newly diagnosed cases of all sites, breast, ovarian and colon cancer by stage (2015)

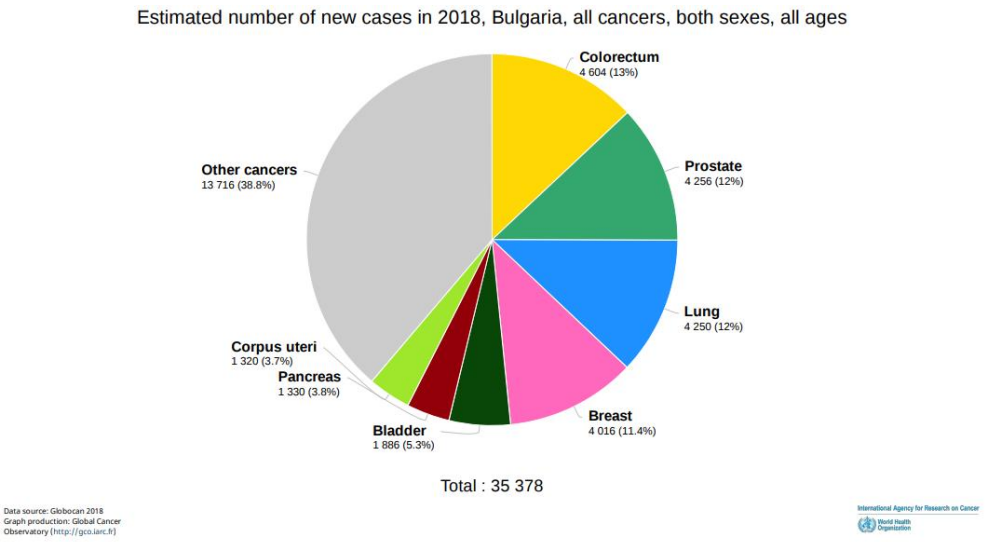

Fig. 10 The estimated number of new cases of cancer, both sexes, all ages, in Bulgaria

(*Source*: *** International Agency for Research on Cancer. GLOBOCAN 2018. *Globocan cancer observatory*. Available from: http://gco.iarc.fr.)

1.2. Prevalence

FRANCE

In 2008, the 5-year partial prevalence of all cancers combined is estimated at 1.1 million people, including 583,580 men and 490,325 women (1). Nearly half of the cases are prostate cancer in men (265,360 cases, or 45%) and breast cancer in women (383,310 or 47%). Colorectal cancer accounts for nearly 10% of all cancers, with 100,240 cases in men and 90,050 cases in women.

The prevalence of individuals with a constitutional mutation in one of the BRCA genes, responsible for hereditary predisposition to breast and / or ovarian cancer (HBOC), is estimated at 2 per 1,000. Lynch syndrome is the most common hereditary predisposition to colorectal cancer, with a prevalence of between 1/800 and 1/1600 for the two main genes, MLH1 and MSH2.

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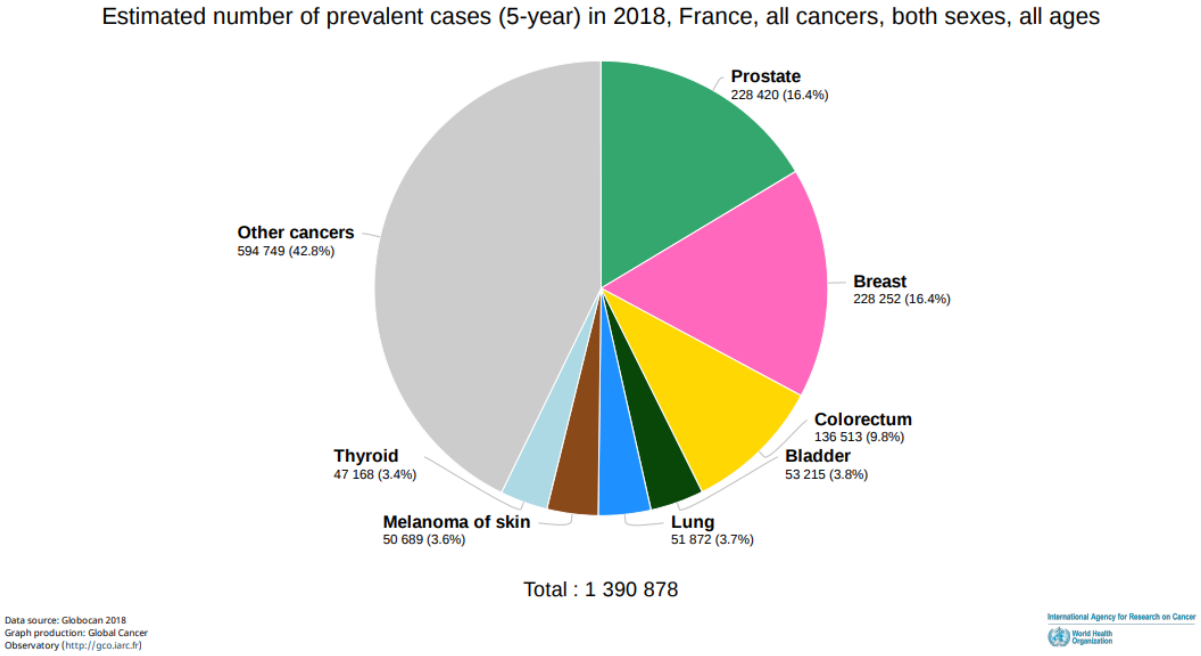

Fig. 11 The estimated number of prevalent cases of cancer, both sexes, all ages, in France (*Source*: *** International Agency for Research on Cancer. GLOBOCAN 2018. *Globocan cancer observatory*. Available from: http://gco.iarc.fr.)

ROMANIA

The 2008 Annual Report of the North-East Regional Registry of Cancer shows a prevalence of cancers in Iasi county of 15.08 per 100,000 inhabitants, which is below the average of the North-East Region (16 / 100,000 inhabitants) and a specific cancer mortality of 207.73 per 100,000 inhabitants, well above the average of the North-East Region (188.38 / 100,000 inhabitants) **[Gheorghiu, 2011]**.

In 2018, IARC published for Romania an estimated number of prevalent cases (5 years) of cancer for both sexes at all ages of 12,334,517 (GLOBOCAN 2018). Case distribution by location indicates that breast cancer was the most common (16.9%), followed by prostate cancer (12.7%), colorectal cancer (11.6%), bladder cancer (5.2%), lung cancer (4.1%), skin melanoma (4%), uterine cancer (3.7%) and other cancers (41.6%) (Fig. 3). Among the other cancers that were recorded we mention: ovarian cancer with 1.6% **[GLOBOCAN 2018]**

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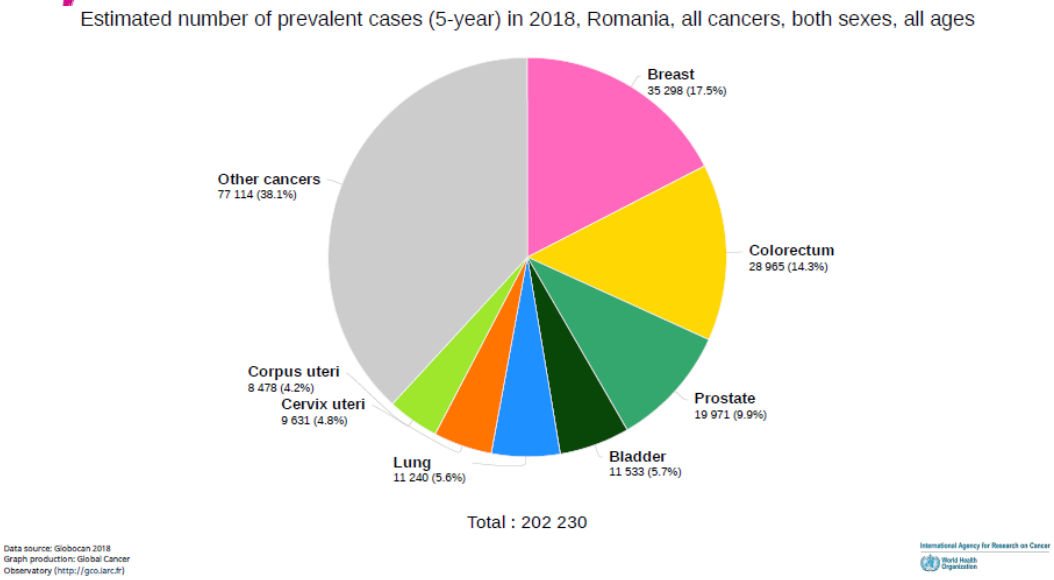

Fig. 12. Estimated number of prevalent cases (5 years) of cancer, both sexes, all ages, in Romania (*Source*: *** International Agency for Research on Cancer. GLOBOCAN 2018. *Globocan cancer observatory*. Available from: http://gco.iarc.fr)

HUNGARY

Table V

Estimated number of prevalent cases in 2018, Hungary, males, all ages

ICD	Cancer	5-year	Proportions***
C00-97	**All cancers**	85 345	1850.9
C61	Prostate	18 340	397.8
C18-21	Colorectum	16 143	350.1
C67	Bladder	7 261	157.5
C33-34	Lung	6 455	140.0
C64-65	Kidney	3 300	71.6
C32	Larynx	2 826	61.3
C00-06	Lip, oral cavity	2 641	57.3
C43	Melanoma of skin	2 501	54.2
C62	Testis	2 392	51.9
C82-86, C96	Non-Hodgkin lymphoma	2 217	48.1
C91-95	Leukaemia	2 082	45.2
C16	Stomach	1 739	37.7
C09-10	Oropharynx	1 697	36.8
C70-72	Brain, nervous system	1 123	24.4
C12-13	Hypopharynx	796	17.3
C25	Pancreas	669	14.5
C73	Thyroid	669	14.5
C15	Oesophagus	668	14.5
C88+C90	Multiple myeloma	563	12.2
C22	Liver	536	11.6

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ICD	Cancer	5-year	Proportions***
C81	Hodgkin lymphoma	517	11.2
C60	Penis	358	7.8
C23-24	Gallbladder	304	6.6
C11	Nasopharynx	214	4.6
C07-08	Salivary glands	200	4.3
C45	Mesothelioma	31	0.67
C46	Kaposi sarcoma	18	0.39

***** Proportions per 100 000**

Table VI

Estimated number of prevalent cases in 2018, Hungary, females, all ages

ICD	Cancer	5-year	Proportions***
C00-97	**All cancers**	99 932	1968.0
C50	Breast	31 217	614.8
C18-21	Colorectum	13 064	257.3
C54	Corpus uteri	6 874	135.4
C33-34	Lung	5 268	103.7
C53	Cervix uteri	4 096	80.7
C73	Thyroid	3 808	75.0
C56	Ovary	3 547	69.9
C67	Bladder	3 094	60.9
C43	Melanoma of skin	3 060	60.3
C64-65	Kidney	2 607	51.3
C82-86, C96	Non-Hodgkin lymphoma	2 321	45.7
C91-95	Leukaemia	1 809	35.6
C16	Stomach	1 275	25.1
C00-06	Lip, oral cavity	1 250	24.6
C70-72	Brain, nervous system	1 188	23.4
C51	Vulva	779	15.3
C09-10	Oropharynx	771	15.2
C25	Pancreas	734	14.5
C32	Larynx	552	10.9
C88+C90	Multiple myeloma	547	10.8
C23-24	Gallbladder	425	8.4
C81	Hodgkin lymphoma	383	7.5
C07-08	Salivary glands	235	4.6
C22	Liver	212	4.2
C52	Vagina	189	3.7
C11	Nasopharynx	132	2.6
C15	Oesophagus	131	2.6
C12-13	Hypopharynx	110	2.2
C45	Mesothelioma	24	0.47
C46	Kaposi sarcoma	8	0.16

*** Proportions per 100 000

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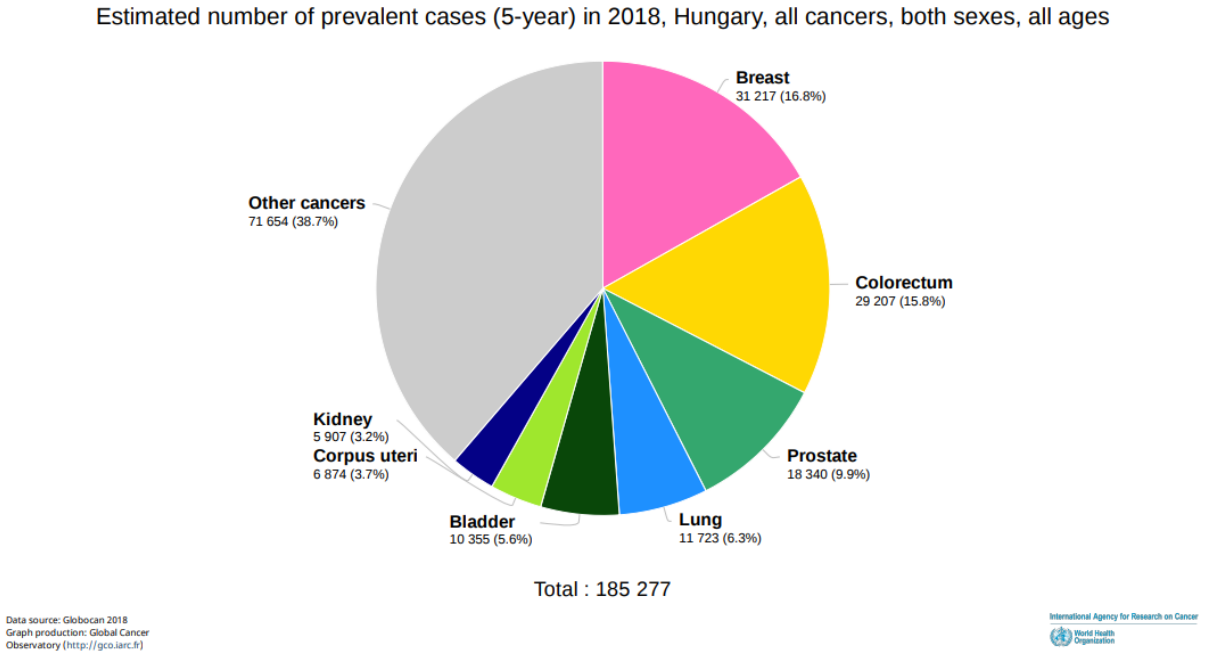

Fig. 13. Estimated number of prevalent cases (5 years) of cancer, both sexes, all ages, in Hungary (*Source*: *** International Agency for Research on Cancer. GLOBOCAN 2018. *Globocan cancer observatory*. Available from: http://gco.iarc.fr)

BULGARIA

The number of cancer patients (all sites) registered in Bulgaria was 284 355 by 2015, which represented a crude prevalence rate 3961.5 per 100 000, i.e. 4% - 4 people out of every 100 were diagnosed with cancer. In females the crude prevalence rate was higher as compared to males - 170 860 and 113 495 cases, respectively, or 4632.4 /100 000 *vs* 3252.4/100 000. The data for crude prevalence rate for colon cancer, breast cancer and ovarian cancer by sex are presented in Table VII.

Table VII
Crude prevalence rate for colon cancer, breast cancer and ovarian cancer by sex in Bulgaria (2015)

	Male		Female		Total	
	Cases	Crude prevalence rate /100 000	Cases	Crude prevalence rate /100 000	Cases	Crude prevalence rate /100 000
Colon cancer	9249	265	9398	254.8	18647	259.8

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Breast cancer	506	14,5	51108	1385.6	51614	719.1
Ovarian cancer			7465	202.4	7465	202.4

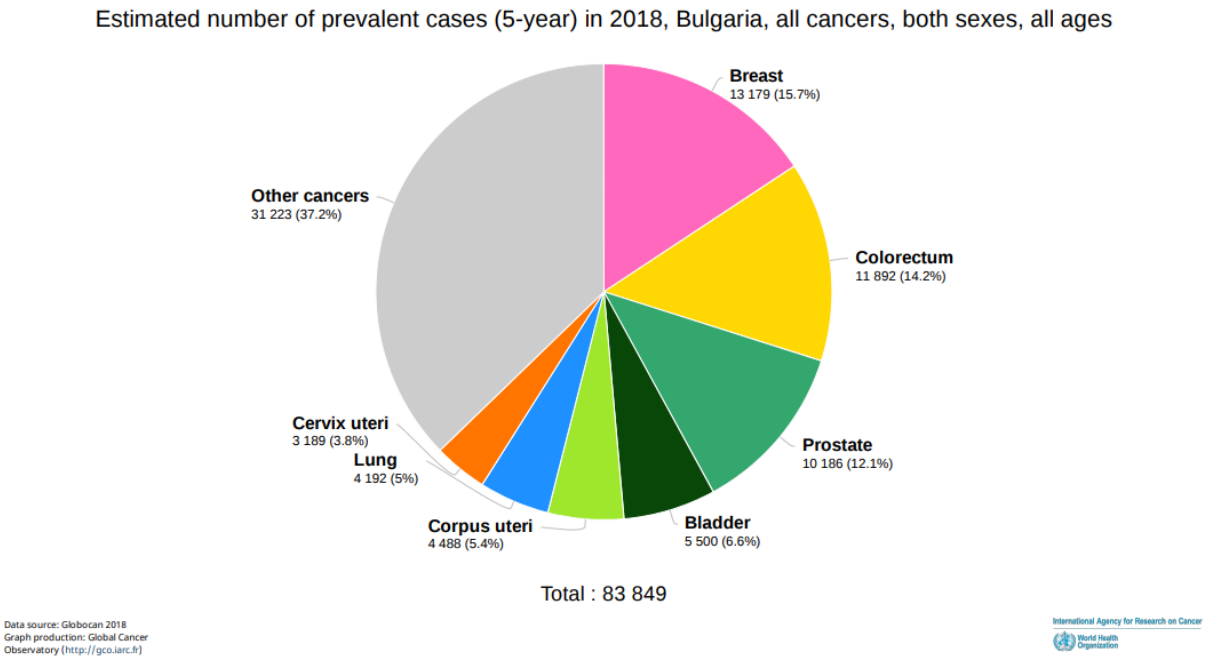

Fig. 14. Estimated number of prevalent cases (5 years) of cancer, both sexes, all ages, in Bulgaria (*Source*: *** International Agency for Research on Cancer. GLOBOCAN 2018. *Globocan cancer observatory*. Available from: http://gco.iarc.fr)

1.3. Risk-Factors

FRANCE

The main modifiable risk factors for cancer include (1):

The tobacco

In France, the number of cancer deaths attributable to tobacco is about 44,000 per year, or 30% of cancer mortality. It is responsible for 93% of lung cancer deaths and significantly promotes the occurrence of other cancers: oral cavity, pharynx, larynx, pancreas, bladder, kidneys, nasal cavity, sinus, esophagus, stomach, liver, uterine cervix, and to a lesser extent myeloid leukemia, colon, rectum, mucinous ovary and breast cancer. The prevalence of active smoking in France is 31.6% of 15-85 year olds.

The alcohol:

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Alcohol consumption is the second leading cause of preventable cancer mortality in France, with 15,000 deaths in 2009 (9.5% of cancer deaths, 12% in men and 6% in women). Alcohol is convincingly associated with cancer risk for the mouth, pharynx, larynx, esophagus, liver, colon-rectum and breast. France remains among the most alcohol-consuming countries in the world and countries of the European Union (11.8 liters of pure alcohol per inhabitant of at least 15 years).

Diet and physical activity:

Dietary or physical activity factors that increase the risk of cancer include alcohol consumption, overweight and obesity (2,300 cancer deaths, 1.6% cancer deaths), consumption of red meat (> 500 g per week) and processed meats, consumption of salt and salted foods, and consumption of food supplements based on beta-carotene. Nutritional factors are responsible for 20 to 27% of cancers in Europe.

Inadequate physical activity is responsible for approximately 2,240 cancer deaths, or 1.6%.

Other cancer risk factors include environmental factors (Radon, ionizing radiation), occupational exposure factors, such as asbestos, and infectious agents such as EBV, HBV, and HCV.

Major non-modifiable risks factors include:

Age

Age is a risk factor for most cancers. The median age to diagnosis of cancer is 68 years of age in men and 67 years of age in women. The aging of the French population is responsible for 33.7% of the increase in cancer incidence in France (1).

About 80 % of breast cancer is declared after 50 years of age (50 % between 50-69 years and 28 % after 69 years), and only 10 % are declared before 35 years (3). Most ovarian cancer is declared after 65 years (5).

Personal history of cancer

For all cancer types combined, after a first malignancy, developing a second cancer is associated with a relative risk (RR) of 1.36 (1). This risk varies with the type of first cancer. For example, the RR is 3-4 for a second breast cancer, and is estimated at 8-10 in the case of

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ductal or lobular carcinoma in situ (3). A personal history of colorectal cancer or advanced adenoma also carries a significant risk of developing a new colorectal cancer (4).

Hormonal factors

Hormonal factors are involved in occurrence of breast and ovarian cancer. The risk of both cancers is higher in women who have not had a child, who have their first child late, and who have early puberty or late menopause (7). Furthermore, taking oral contraceptives or hormonal treatments for menopause may also increase the risk of breast cancer, which is modulated by the duration of treatment (8).

Family history of cancer

A familial history of breast cancer in a first degree relative gives an RR of 2 (3). This risk increases with the number of first degree relatives affected and the age of occurrence. A first-degree relative with ovarian cancer gives an RR of 3 for developing ovarian cancer in the absence of a predisposing mutation in BRCA1 or BRCA2.

A first degree relative with colorectal cancer exposes to a RR at 2.25. As for breast cancer, this risk increases with number of relatives with colorectal cancer and age of occurrence (6).

Hereditary cancer predisposition

Hereditary predisposition concerns 5 to 10 % of cancers, with high to very high risk of cancer according to the syndrome. More than 50 syndromes have been described, the most common of which are listed below (9).

Genetic predisposition	Major associated genes
Breast/ovarian syndrome	BRCA1,BRCA2,PALB2,RAD51
Lynch syndrome	MLH1,MSH2,MSH6,PMS2,EPCAM
Familial pituitary adenomas	AIP
Ataxia–telangiectasia	ATM
Hereditary diffuse gastric cancer	CDH1
Hereditary papillary renal cancer	MET,FH
Hyperparathyroidism	CASR,CDC73
Cowden syndrome	PTEN,PICK3CA,AKT1
Fanconi syndrome	FANC

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Von Hippel-Lindau disease	VHL
Familial malignant melanoma	CDKN2A,MITF,BAP1,POT1,CDK4
Endocrine neoplasia	MEN1,RET,CDKN1B
Neurofibromatosis	NF1,NF2,LZTR1,SMARCAB1,SPRED1,SMARCE1
Paraganglioma – pheochromocytoma	SDH,TMEM127,MAX,EPAS1
Familial polyposis adenomatous	APC,MUTYH,POLE,POLD1,NTHL1
Retinoblastoma	RB1
Birt hogg-dubé syndrome	FLCN
Bloom syndrome	BLM
Carney syndrome	PRKAR1A,ARMCS
Gorlin syndrome	PTCH1,PTCH2,SUFU
Li-Fraumeni syndrome	TP53
Numegen syndrome	NBN
Peutz Jeghers syndrome	STK11
Juvenile polyposis syndrome	BMPR1A,SMAD4
Werner syndrome	WRN
Xeroderma pigmentosum	XP

ROMANIA

A study by Matei M et al. in 2009, regarding the risk factors for genital neoplasia (ovarian cancer, uterine cancer and cervical cancer) among women of the North-East region of Romania, identified the pathological history as associated with an increased risk (with statistical significance) as well as fertilization treatment or BMI over 25 Kg / m2 (without statistical significance) **[Matei et al, 2009]**. In another study developed in the same region of the country, the authors identified the following factors associated with an increased risk of developing ovarian cancer: age (OR = 12.44; p <0.01x10-5) (58.63% of cases were diagnosed at ages between 50 and 69 years, which means during postmenopausal period); origin in urban area (OR = 3.45; p = 0.04x10-3); ovulatory period over 30 years (OR = 10.84; p <0.01x10-5) and age at diagnosis (OR = 2.01; p=0,016x10^{-3}). In contrast to most research founded in the literature, the authors did not identify the early age at first menstruation, late menopause, obesity, smoking, and high socioeconomic status as factors that increase the risk for ovarian

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malignancies, although the results of the current study were in agreement with some conclusions published by other authors **[Matei et al, 2010]**.

1.4. Mortality

FRANCE

In 2012, cancer mortality was estimated at 148 000 deaths, including 85 000 deaths in men and 63 000 in women (1). Lung cancer was the leading cause of cancer death in men (21,236 deaths), followed by colorectal cancer (9,275 deaths) and prostate cancer (8,876 deaths). Breast cancer was the leading cause of cancer death in women (11,886 deaths), followed by lung cancer (8,623 deaths), colorectal cancer (8,447 deaths) and ovarian cancer (3,140).

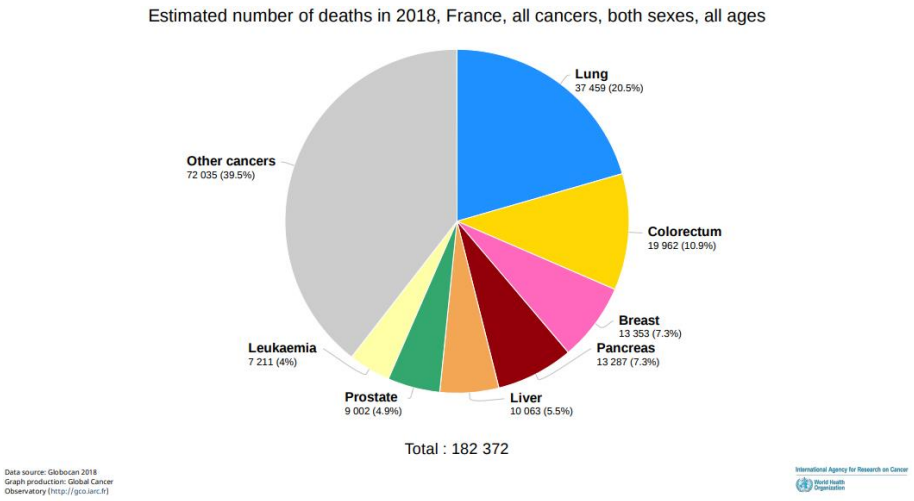

Fig. 15. Estimated number of deaths cases (5 years) of cancer, both sexes, all ages, in France (*Source*: *** International Agency for Research on Cancer. GLOBOCAN 2018. *Globocan cancer observatory*. Available from: http://gco.iarc.fr)

ROMANIA

In terms of mortality, in Romania, in 2008, ovarian cancer ranked the 7th position, with a rate of 5.2 deaths / 100,000 women (Fig. 15) **[GLOBOCAN 2008]**. A rate of 8.23 deaths per 100,000 women (which far exceeds the country average) was recorded for North-East Region. **[Gheorghiu, 2011]**.

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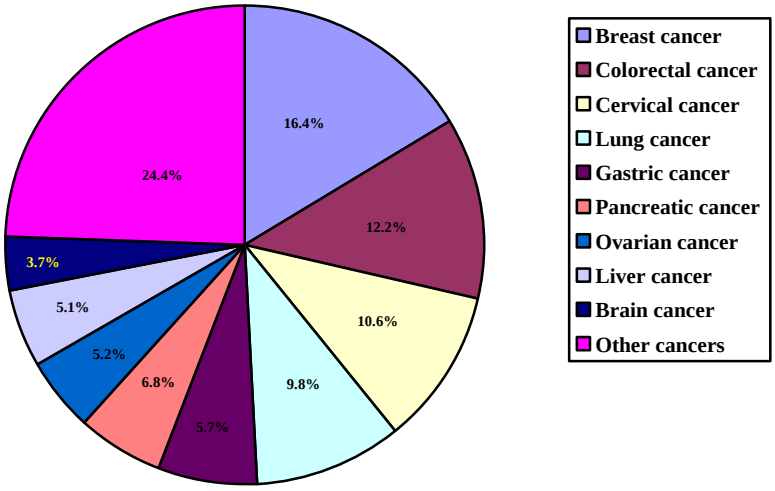

Fig. 15. Mortality (standardized by age) for the main types of cancers developed by women in Romania, 2008

According to the International Agency for Research on Cancer (IARC), in Romania, in 2018, the estimated total number of cancer deaths for both sexes at all ages was 50,902 (GLOBOCAN 2018). Deaths distribution by location indicates that lung cancer was on the first place (20.2%), followed by colorectal cancer (12.4%), breast cancer (6.6%), liver cancer (6.2%), gastric cancer (5.9%), pancreatic cancer (5.8%), prostate cancer (4.9%) and other cancers (38%) (Fig. 5). Among the other cancers that were recorded we mention: ovarian cancer (2.3%) and uterine cancer (1.5%) **[GLOBOCAN 2018]**.

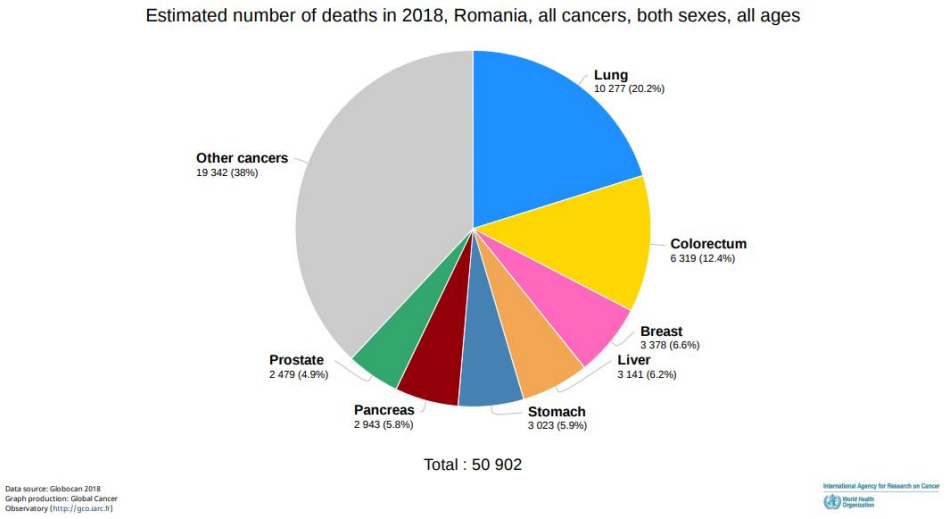

Fig. 16. Estimated number of cancer deaths, both sexes, all ages, in Romania

(*Source*: *** International Agency for Research on Cancer. GLOBOCAN 2018. *Globocan cancer observatory*. Available from: http://gco.iarc.fr.)

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HUNGARY

Table VIII
Estimated number of deaths in 2018, Hungary, females, all ages

ICD	Cancer	Number	Uncertainty interval	Crude Rate*	ASR (World)*	Cum. risk**
C00-97	**All cancers**	15 424	[15126.6-15727.3]	303.7	122.0	-
C33-34	Lung	3 535	[3367.8-3710.5]	69.6	30.9	-
C50	Breast	2 212	[2055.7-2380.1]	43.6	17.9	-
C18-21	Colorectum	2 209	Not available	43.5	14.8	-
C25	Pancreas	1 109	[1021.9-1203.5]	21.8	7.9	-
C56	Ovary	777	[701.4-860.7]	15.3	6.6	-
C16	Stomach	628	[561.0-703.0]	12.4	4.3	-
C53	Cervix uteri	499	[438.7-567.6]	9.8	5.1	-
C91-95	Leukaemia	434	[374.2-503.4]	8.5	3.4	-
C54	Corpus uteri	413	[359.6-474.3]	8.1	2.9	-
C23-24	Gallbladder	392	[343.0-448.0]	7.7	2.5	-
C64-65	Kidney	373	[318.9-436.3]	7.3	2.6	-
C70-72	Brain, nervous system	342	[283.6-412.4]	6.7	3.4	-
C67	Bladder	301	[257.1-352.3]	5.9	2.0	-
C22	Liver	292	[238.6-357.4]	5.8	2.1	-
C82-86, C96	Non-Hodgkin lymphoma	286	[233.9-349.7]	5.6	2.1	-
C43	Melanoma of skin	182	[148.7-222.8]	3.6	1.5	-
C00-06	Lip, oral cavity	145	[109.1-192.6]	2.9	1.3	-
C88+C90	Multiple myeloma	142	[111.4-181.0]	2.8	1.0	-
C51	Vulva	106	[79.6-141.2]	2.1	0.66	-
C15	Oesophagus	99	[71.2-137.7]	1.9	0.88	-
C09-10	Oropharynx	73	[57.1-93.3]	1.4	0.76	-
C32	Larynx	70	[50.0-98.0]	1.4	0.75	-
C73	Thyroid	65	[50.2-84.1]	1.3	0.42	-
C12-13	Hypopharynx	39	[28.1-54.1]	0.77	0.39	-
C52	Vagina	32	[22.1-46.4]	0.63	0.22	-
C07-08	Salivary glands	23	[14.9-35.4]	0.45	0.19	-
C11	Nasopharynx	19	[11.8-30.5]	0.37	0.22	-
C45	Mesothelioma	16	[9.5-26.9]	0.32	0.14	-
C81	Hodgkin lymphoma	16	[9.4-27.2]	0.32	0.19	-
C46	Kaposi sarcoma	1	[0.50-1.9]	0.02	0.00	-

* Crude and age-standardized rates per 100 000

Table IX
Estimated number of deaths in 2018, Hungary, males, all ages

ICD	Cancer	Number	Uncertainty interval	Crude Rate*	ASR (World)*	Cum. risk**
C00-97	**All cancers**	17 586	[17271.4-17906.3]	381.4	203.2	-
C33-34	Lung	5 358	[5145.6-5579.2]	116.2	62.9	-
C18-21	Colorectum	2 867	Not available	62.2	31.2	-

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ICD	Cancer	Number	Uncertainty interval	Crude Rate*	ASR (World)*	Cum. risk**
C61	Prostate	1 225	[1134.9-1322.2]	26.6	11.8	-
C25	Pancreas	969	[868.0-1081.8]	21.0	11.2	-
C16	Stomach	895	[800.5-1000.7]	19.4	9.9	-
C67	Bladder	649	[568.9-740.3]	14.1	6.8	-
C22	Liver	628	[556.7-708.5]	13.6	7.3	-
C15	Oesophagus	493	[414.9-585.8]	10.7	6.3	-
C00-06	Lip, oral cavity	461	[394.6-538.6]	10.0	6.1	-
C64-65	Kidney	458	[396.6-529.0]	9.9	5.3	-
C32	Larynx	456	[400.5-519.2]	9.9	5.7	-
C91-95	Leukaemia	438	[382.1-502.1]	9.5	5.2	-
C70-72	Brain, nervous system	354	[299.1-418.9]	7.7	4.8	-
C12-13	Hypopharynx	320	[274.8-372.6]	6.9	4.3	-
C82-86, C96	Non-Hodgkin lymphoma	299	[256.3-348.8]	6.5	3.5	-
C09-10	Oropharynx	267	[220.2-323.7]	5.8	3.7	-
C23-24	Gallbladder	216	[179.0-260.6]	4.7	2.3	-
C43	Melanoma of skin	169	[131.6-217.0]	3.7	2.0	-
C88+C90	Multiple myeloma	138	[108.8-175.0]	3.0	1.5	-
C62	Testis	42	[30.6-57.6]	0.91	0.70	-
C11	Nasopharynx	42	[30.7-57.5]	0.91	0.54	-
C07-08	Salivary glands	37	[26.2-52.2]	0.80	0.45	-
C60	Penis	31	[21.5-44.7]	0.67	0.34	-
C73	Thyroid	30	[20.5-44.0]	0.65	0.32	-
C45	Mesothelioma	25	[16.6-37.7]	0.54	0.31	-
C81	Hodgkin lymphoma	22	[14.2-34.2]	0.48	0.33	-
C46	Kaposi sarcoma	2	[0.90-4.4]	0.04	0.02	-

* Crude and age-standardized rates per 100 000

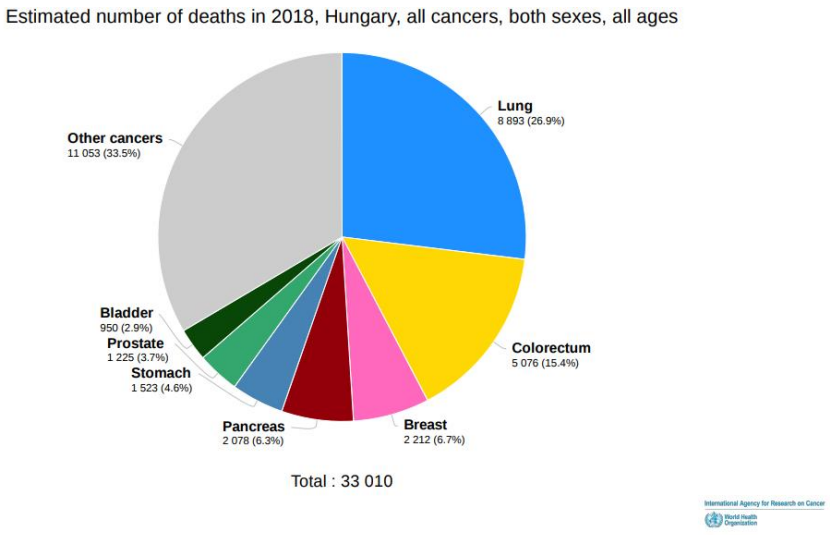

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Fig. 17 Estimated number of cancer deaths, both sexes, all ages, in Hungary

(*Source*: *** International Agency for Research on Cancer. GLOBOCAN 2018. *Globocan cancer observatory*. Available from: http://gco.iarc.fr.)

BULGARIA

BNCR data show that the number of cancer deaths in 2015 was 17932, which represented a crude mortality rate of 249.8/100 000 people. In men this index was higher - 10412 cases, or 298.4/100000, as compared to that of women – 7520 cases, or 203.9/ 100 000.
Mortality due to colon cancer was higher in males – 954 cases, 27.3/ 100 000 as compared to females – 738 cases, 20/100 000 inhabitants. A considerably higher mortality rate was observed in breast cancer of women - 1312 cases, or 35.6/100 000. Mortality due to ovarian cancer was lower - 438 cases, or 11.9/100 000 .

The five-year relative survival for breast, ovarian and colon cancer patients >15 years of age diagnosed in the period 2000-2007 in Bulgaria are presented in Table X according to EUROCARE-5 data (last update 5 March, 2014).

Table X

Five-year relative survival (%) for breast, ovarian and colon cancer patients by sex

	Number of cases		5-year relative survival			Difference from the European average
	Males	Females	Males	Females	All	
All sites	62313	59218	29.4	51.2	40.2	-14.4
Colon cancer	5266	4605	45.0	45.3	45.2	-10.4
Breast cancer	176	16802	57.2	72.8	72.6	-11.1
Ovarian cancer	-	3777	-	40.6	40.6	-0.2

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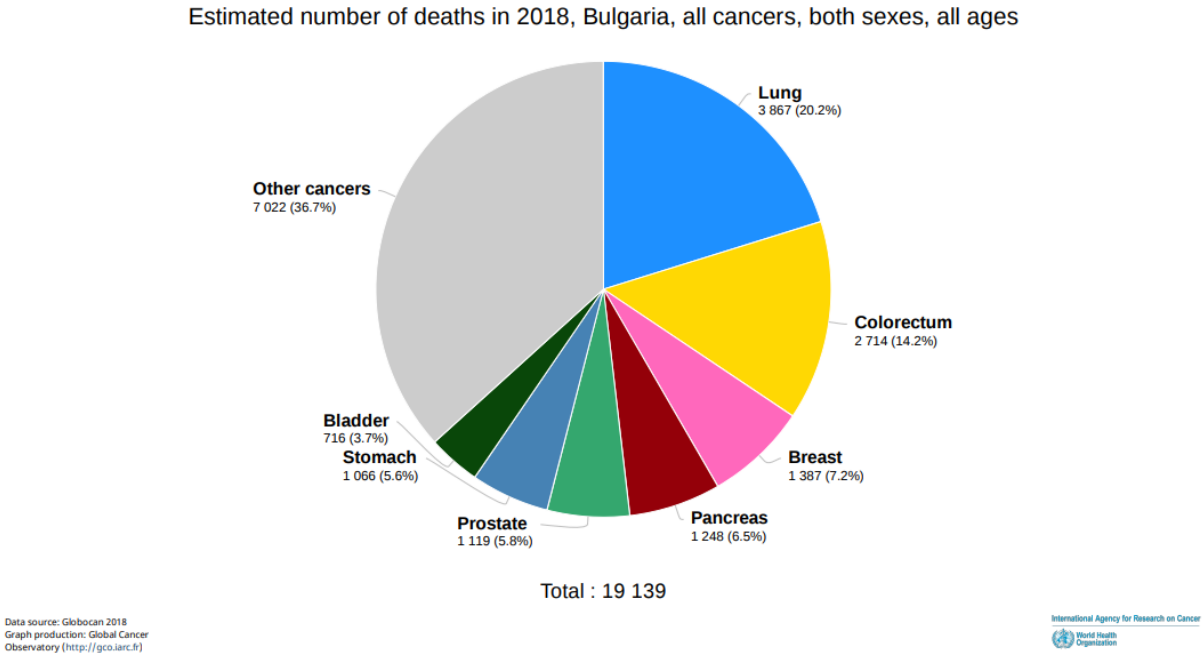

Fig 18. Estimated number of cancer deaths, both sexes, all ages, in Bulgaria

(*Source*: *** International Agency for Research on Cancer. GLOBOCAN 2018. *Globocan cancer observatory.* Available from: http://gco.iarc.fr.)

2. Current situation of the National Strategies in models of genetic risk assessment for hereditary cancer (HBOC, CRC and other types) in each country involved as a partner in the HOPE project (Table XI).

Country / National Strategies regarding the models of genetic risk assessment for hereditary cancer	**FRANCE**	**ROMANIA**	**HUNGARY**	**BULGARY**
	- The High Health Authority has published criteria for genetic testing of patients referred to an oncogenetics	**- NO strategies** - Prospective study conducted at Institute of Oncology Cluj Napoca that evaluated the performance of the **Myriad risk assessment**	- There are **no national approved risk assessment models** available in Hungary - ***BRCA1*** **and** ***BRCA2*** **gene tests**	**No strategies**

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	consultation for suspected HBOC - **Manchester score** or the **BOADICEA score** - most frequently used in France to determine HBOC risk - for personal or familial history of Lynch syndrome-related cancers, the **Bethesda** and **Amsterdam criteria** are used - there are national recommendations for neuroendocrine tumors	**model** for 250 high-risk breast cancer pts tested for BRCA1/2 mutations between February 2015 and December 2016 at IOCN - Myriad genetic risk assessment model CAN BE an acceptable tool for determining the risk of carrying BRCA mutations in Romanian population if the score is between 10-20%	**have been provided by the Molecular Genetics Department of National Oncology Institute, Budapest, Hungary for nearly 20 years** for families with hereditary defects -	

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3. Current practical situation in Genetic Testing Availability for HBOC and CRC in each country involved as a partner in the HOPE project (Table XII).

Country / Genetic Testing Availability for HBOC and CRC	**FRANCE**	**ROMANIA**	**HUNGARY**	**BULGARY**
	- the diagnosis of an inherited predisposition to cancer is based on **the national oncogenetic plan** = **148 consultations in 104 cities**, and **25 laboratories** - The main consultations are from Cancer Center and Public Hospital - Doctors from main consultations can make advanced consultations in peripheral cities - The National Cancer Institute on his web site have a link to the coordinates of each oncogenetics center and theirs doctors - 25 French accredited	- According to "*Cancer Screening in the European Union Report on the implementation of the Council Recommendation on cancer screening*" in Romania the **access to genetic testing is provided by a pharmaceutical company** - **Acording to ROHEALTH survey (2019):** *** 2 institutions reported availability of hereditary cancer genetic testing for diagnosis** (1 private entity + 1 governmental entity both from Timisoara). * 5 (4 private + 1 governmental) entities **provide genetic testing for breast/ovarian and**	- Genetic tests and genetic counselling for hereditary cancers are available in Hungary, **BUT** it is centralized in our capital Budapest - **3 public institutions** provide genetic tests	- genetic tests for hereditary colon cancer, ovarian cancer and breast cancer = provided by private laboratories - most of these tests are performed abroad and the time needed to have the results = weeks to months - genetic counseling from a specialist in medical genetics = is missing - when the patients get their results

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	laboratories (38 606 analysis in 2016). - Each laboratory has its own specialty, but all are able to test HBOC and/or CCR. - all genetic predispositions currently known to cancers can be tested within these 25 laboratories	**colorectal cancer**.		

4. The situation of the current Research Programs on mutation screening and founder mutation detection for HBOC and CRC in each country involved as a partner in the HOPE project (Table XIII).

Country / Research Programs on mutation screening and founder mutation detection for HBOC and CRC	**FRANCE**	**ROMANIA**	**HUNGARY**	**BULGARY**
				- research performed at the Center for Molecular Medicine, Sofia
		- 7 Project (4 national + 3 international)		**- 1 National Project** "Personalized Innovative Medicine (PERIMED)" - project in the field of oncology, genetics, personalized medicine and pharmacogenetics.
		1. Systematic evaluation of		

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		genetic risk factors associated with breast cancer in female (BrCa), colon and rectum (CRC), prostate (PrCa) and lung (LuCa) cancers		
		2. Genetic prostate cancer variants as biomarkers of disease progression		
		3. BRCA1 and BRCA2 Mutation in Romanian Population: a Study of Genotype - Phenotype Correlation at Diagnosis With Prospective Disease Outcome and Survival		
		4. Optimization and implementation of molecular biology technology in detection of breast and ovarian cancer hereditary predisposition		
		5. Comparative study of gene expression, in healthy and tumoral		

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		tissues, in carriers of mutations and polymorphisms of predisposition genes to breast and ovarian cancer		
		6. Development of a multi technological approach to evaluate the hereditary risk to colorectal cancer		
		7. Involvement of oncogenetics activities within the project "The East European Network of Excellence for Research and Development in Chronic Diseases CHRONEX-RD"		

FRANCE

A variety of research programs focused on the exploration of hereditary predisposition to breast and / or ovarian cancer and colorectal cancer are currently supported by the National Cancer Institute. The diversity of pathogenic variants observed in French HBOC and CCR families has shown that targeting founder mutations is not appropriate for this population.

Five programs concern HBOC (19):

TUMOSPEC

This national program aims to determine the tumor spectrum and the penetrance of genes that are known or suspected to be involved in hereditary predisposition to breast and ovarian cancer. A panel of 24 genes is analyzed, and potentially pathogenic variants are followed by segregation analysis in appropriate families.

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COVAR

This program aims to resolve the classification of variants of unknown significance in the BRCA1, BRCA2 and PALB2 genes as either pathogenic or neutral for cancer risk. The program is a segregation study proposed to family members of probands discovered to carry variants in these genes.

GEMO:

This program aims to identify modifier genes in carriers of pathogenic variants in the BRCA1 or BRCA2 genes which could explain inter- and intra-familial variability in the occurrence of breast and / or ovarian cancer.

SIGNAL:

This study aims to identify genetic determinants of resistance / sensitivity and / or toxicity to adjuvant therapy and genetic determinants predisposing to breast cancer:

- determinants of resistance or sensitivity after adjuvant therapy including Herceptin®
- determinants of cardiac toxicity after adjuvant therapy including Herceptin®
- genetic determinants predisposing to different types of breast cancer: HER2 +, triple negative, RH +
- genetic determinants predisposing to breast cancer

SAO3:

This study aims to assess the incidence of constitutional mutations in breast cancer predisposition genes (BRCA1, BRCA2, PTEN and PALB2) in patients with triple-negative breast cancer.

Three programs concern predisposition to CCR (19):

DOCC:

The objective of this study is to compare the frequency of genetic variations and to evaluate the association of these variations with the occurrence of colorectal cancer in patients with increased risk of colorectal cancer.

GENCOLON:

The objective of this study is to determine whether gene mutations found more often in people with colorectal cancer than in healthy individuals could be associated with the development of colorectal cancer.

MYH:

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This is a study to evaluate the risk of colorectal polyposis in patients with mono-allelic mutation of the MUTYH gene.

HUNGARY

The first evidence of genetic defects inherited in families can be a reason for some hereditary tumor disorders was suggested by Mary Claire King an American geneticist. The possible site of *BRCA1* (BReastCAncer 1- the first "breast cancer gene") located on the long arm of the 17 th chromosome has been suggested by M.C. King. Discovery of *BRCA2* (BReastCAncer 2- the second “breast cancer”) gene took one more year to be described. Germline mutations in the highly penetrant cancer susceptibility genes, *BRCA1* and *BRCA2* are associated with a high lifetime risk of breast and ovarian cancer. Novel scientific results has been obtained in the last two decades about the function of *BRCA* genes and the risk of *BRCA* induced tumor formation in families carrying *BRCA* mutations.

Gene products of *BRCA* genes interact with different proteins in order to repair double-stranded brakeage of DNA, activation of checkpoints of the cell cycle and participate activation of a response to DNA damage.

Genetic testing related to inherited mutations of *BRCA* genes and risk assessment in framework of genetic counselling makes it possible to identify risk-averse people, thereby promoting early diagnosis, risk reduction, and proper therapeutic decisions. **The Research Group of Professor Edit Olah** joined to an international consortium in 1992 to get insight into the genetic background of hereditary breast and ovarian cancer. **Olah’s group has been providing *BRCA1* and *BRCA2* gene tests for nearly 20 years** for families with hereditary defects in case of more than one breast or ovarian cancer on the same branch of the family or even one male breast cancer and also when the diseases are detected especially in young age (under 40 years). Genetic counselling and genetic tests are collaborated by a multidisciplinary team composed of clinical and molecular geneticists, clinical oncologists, breast surgeons, gynaecologists, human genetic assistants, psychologists in **Budapest, Hungary at the Molecular Genetics Department of National Oncology Institute.** The genetic tests are financed by the Hungarian National Health Insurance Company.

Department of Molecular Genetics of National Oncology Institute at the Institute of Health Sciences in Budapest Hungary is the *BRCA1* and *BRCA2* National and International Reference Center for investigations. Nearly **9,000 genetic tests** have been carried out in order

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to detect hereditary cancers **since 1995**. Hungarian experiences are now demonstrated with a focus on breast and ovarian cancer syndromes.

The incidence and penetrance of BRCA 1 and 2 inherited mutations in Hungary

Ninety- ninety-five percent of breast cancers are not due to the *BRCA1* and *BRCA2* disease causing variants. **In Hungary 5–7% of breast cancers and 15 % of ovarian cancers can be associated with *BRCA1* and *BRCA2* genes with definitive mutations.** However, even hereditary (often with familiar appearance) breast cancers are connected with further somatic mutations and non-genetic factors. A complex, multi-tiered stream of carcinogenesis still remain unknown.

BRCA1 and *BRCA2* genes of germline inheritance with other genetic and environmental factors and lifestyle can possibly be responsible for the hereditary breast and ovarian cancer syndromes (HBOC).

Following features are main indicators for HBOC:

-cumulative incidence of breast or ovarian cancer in a family on the same branch;
-juvenile breast cancer (the most common of hereditary tumors);
-often multi-focal, bilateral or multiple primary tumors can be found in a patient;
-other cancers: male breast cancer and rarely prostate, pancreatic cancer;
- Ashkenazi Jewish (Eastern European) ancestry;
-Triple Negative breast cancers (<60y)

Due to autosomal dominant inheritance there is 50% chance of passing the mutated allel into the offspring. A woman can still be a mutant *BRCA* allel carrier even if never turned on her female branch of the family since the defective allel can be derived from her father's side. The average cumulative risk of *BRCA1* and *BRCA2* mutation carriers are 56-87% in case of breast cancer and 27-44% of ovarian cancer respectively up to the age of 70 years. Complete penetrance of *BRCA1* and *BRCA2* mutations cannot be observed so other genetic and environmental factors may also influence the risk of the diseases. Studying gene-environment interactions nowadays are a popular research interest. The cumulative risk of diseases was compared to the randomly selected population involving in Hungarian data: significantly lower risk has been found in the random population than in the disease associated one. According to these studies, the *BRCA1* mutation caused carcinoma

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risk is in average 65% for breast cancer, 39% for ovarian cancer and *BRCA2* risk is 45% for breast cancer and 11% for ovarian cancer, respectively.

BRCA1 carriers manifest disease at younger (43 year old) age than *BRCA2* mutation carriers (47year old). Edit Olah's working group detected that approximately 90% of *BRCA* mutation carriers develop breast cancer before their age of 50 and there is no difference between *BRCA* mutation's carriers or not being a carriers for ovarian cancer in Hungary. Breast cancer patients with *BRCA1* or *BRCA2* mutations develop the second primer tumor in the opposite breast have increased risk of approximately with a 3-5% of annual risk which means 17% in 5 years, 30-40% in 10 years.

Danger of contralateral breast cancer development is lower at the age of over 50 years with *BRCA2* mutation than with *BRCA1* mutations.

In Hungary both genes, but especially *BRCA2* are responsible for the relative risk of male carriers for the disease in 6 % . However male breast cancer is rare, *BRCA* caused tumor was found in 0.1-0.2%. According to the Hungarian data (E. Olah) the *BRCA2* mutations are responsible for more than 20% of male breast cancer.

BRCA1 and *BRCA2* mutation carriers have additional other tumor risks too. Male *BRCA2* mutation carrier HBOC syndrome patients have higher risk of developing prostate cancer under the age of 65 (up to 20 times greater than relative risk to the average population). There is an increased risk of pancreatic cancer, too.

The breast cancer of *BRCA1* mutation carriers is mainly called triple negative (estrogen receptor negative, progesteron receptor negative, ERBB2 / HER2 negative) belongs to the basal (CK5 / 6 +) subtype. *BRCA1* mutation is justified in every fourth basal breast cancer. Molecular characteristics of breast cancer of *BRCA2* mutation carriers are practically the same compared to sporadic breast cancer's patients. Although familiar hereditary breast cancer syndromes are the most commonly occurring because of *BRCA1* and *BRCA2* inherited mutations (> 80%), but other hereditary syndromes can also be associated with increased level of breast and ovarian cancer risk.

Besides the *BRCA* mutations, high risk of breast cancer is associated with *TP53, PTEN, STK11, CDH1* hereditary gene mutations carrying allels in the germ line. The rest of potential breast cancer predisposing genes have unknown frequency and only a moderate (2-3-fold) risk-increasing effect.

The aforementioned genes of rare cancer syndromes take place in less than 1% compared to breast cancer families. Mutation spectrum of *STK11* gene has been published from colon

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polyps and malignomas affected Hungarian families. Beside *STK11* and *BRCA1*, *BRCA2*, other genes have already been suggested for familiar adenomatosis polyposis syndrome like *APC, ATM, BAP1, BARD1, BMPR1A, BRIP1, CDH1, CDKN2A CDK4, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH6, MITF, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4,* and *TP53***.** The role of *STK11* gene of breast cancer at young age has been studied and currently being evaluated at the Molecular Genetics Department of National Oncology Institute.

The Lynch syndrome (also called hereditary nonpolyposis colorectal cancer, HNPCC) is also characterized in this Institute since HNPPC and ovarian cancer might appear together.

The mutations of HNPCC /Lynch syndrome's gene called *EPCAM / TACSTD1* have been discovered and also first published by E. Olah's team in Hungary. Twenty-five -thirty percent of familiar breast cancer carcinoma can be explained by the so-called "breast cancer genes" known today, however some predisposing genes are still hidden. Together with CIMBA (Consortium of Investigators of Modifiers of *BRCA 1* and *BRCA2*) many new predisposing genes and population specific frequent variants have also been published by E. Olah. These variants are low risk variants but combined their occurrence can significantly change *BRCA1* and *BRCA2* risk carriers.

[Based on: **Oláh E, Mátrai Z: Herediter emlő- és petefészekrák-szindróma, a gyanútól a rizikócsökkentésig. MC Medicina Chapter 15. 389-408]**

5. List of institutions, cancer centers, etc. that provide genetic testing and counselling services in each country involved as a partner in the HOPE project (Table XIV).

Country / Institutions/ Cancer Centers	**FRANCE**	**ROMANIA**	**HUNGARY**	**BULGARY**
Institutions / cancer centers providing Genetic testing	- 2017 = 77 478 patients have benefited from a consultation (8% increase in the number of consultations compared to 2016).		Molecular Genetics Department of National Oncology Institute, Budapest, Hungary	**5** public institutions
Institutions /		**ROHEALTH**		**9** public and private

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cancer centers providing Genetic counselling	- The whole territory is covered by the oncogenetic plan. - The average time of consultation is 12 weeks for probands and 6 weeks for the related. - About 29 500 probands have benefited from genetic analysis. - Among the probands, 92 % have been analysed using panel sequencing - **The French expert groupe "Genetic et Cancer"** determined the genes to be included in a panel analysis for HBOC indication: BRCA1, BRCA2, PALB2, RAD51C, RAD51D, CDH1, TP53, PTEN, MLH1, MSH2, MSH6, PMS2, and EPCAM.	**survey:** **2 cancer genetic counselling centers (Iasi and Timisoara)**		institutions (Universities, Hospitals, and Private laboratories)

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6. The situation of Education Programs regarding Oncogenetics in each country involved as a partner in the HOPE project (Table XV):

Country / Education Programs	FRANCE	ROMANIA	HUNGARY	BULGARY
Postgraduated courses		**For doctors = 2**		Oncogenetics = part of the postgraduate courses in medical genetics and medical oncology specialties
Conferences / Congresses		**For students = 2**		"The Multidisciplinary Oncology Talks and Extracts" (abbreviation in Bulgarian = MORE) - organized by the Bulgarian Oncological Scientific Society
Web page		www.oncogenetica.umfiasi.ro **General population = 1**		
Brochure		**Oncogenetic information brochure for doctors = 1**		
Leaflets		**Oncogenetic information leaflet for patients = 1**		

FRANCE

6.1. Oncogenetics Training Programs for Health Care Professionals and Medical Specialists

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These programs include university diploma courses and continuing education programs. They are intended for all health professionals, and particularly for doctors treating cancer patients, in order to provide appropriate care. These programs include:

- Inter-University Diploma "Oncogénétique" proposed by Paris-Descartes University, in collaboration with other Parisian schools of medicine. This training includes the general principles of oncogenetics, the molecular mechanisms involved, clinical diagnostic and testing criteria, and the management of patients. The course content is updated annually (21).

– The national genetics conference ("Assises de Génétique"), held every two years in France, presents new discoveries and progress in medical genetics and medical practices. Oncogenetics is well represented at these conferences (22).

– Oncogenetics teaching is carried out during the training of interns of medical genetics, during their four years of study as part of the specialized medical genetics degree.

- Two very high output sequencing pilot platforms have been created in France. These platforms propose to perform whole-exome-sequencing and whole-genome sequencing analyzes in a diagnostic and theranostic setting in oncology. In order to train non-geneticist prescribers in this type of analysis, a short 30-minute training is proposed, dealing with the general principles of hereditary predisposition to cancer, as well as the ethical and regulatory aspects to be respected within the framework of an analysis of the genetic characteristics of an individual. Continuing professional development, lasting 7 hours, will complete this training.

Medical genetics is taught in 2nd and 3rd years of medical studies in all schools of Medicine in France. The program is based on the French College of Medical Genetics, and includes training in clinical genetics, oncogenetics, chromosomal and molecular genetics. The teaching of oncogenetics continues through the 6th year of medical studies, in order to prepare for the national classification examination in 6th year, giving access to the status of medical resident. The teaching program is integrated into the national college of medical oncology, and concerns the identification of the main syndromes of hereditary predisposition to cancer by organ, the genes involved in these predispositions, as well as the management of HBOC and Lynch syndrome patients. University education in oncogenetics is also offered to paramedical disciplines, thus integrating during the studies of midwives, nurses and pharmacy.

6.2. Health Education Programs for patients and their families at risk for hereditary cancer

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Associations of patients and their families with hereditary predisposition to cancer have been formed. Most hereditary predispositions to cancer are attached to an association, which are frequently sponsored by medical specialists and provide information on the progress of oncogenetic consulation, the modes of transmission and the management recommended for patients. HBOC families may join for example the associations BRCAFRANCE (23) or GENETICANCER (24). HNPCC-Lynch association (25) and Familial Adenomatous Polyposis association (26), among others, are open to those with predisposition to digestive cancers.

Information booklets are also available in oncogenetic consultations in France.

6.3. Health Education Programs for the General Public

The French National Institute of Cancer presents open access educational programs for the general public, mainly concerning HBOC and Lynch syndrome.

ORPHANET (26) is an international information portal dedicated to rare diseases, created in France in 1996. This portal includes open access information documents intended for the general public, including diseases predisposing to cancer.

The website "Oncogenetique", anticipated in 2019, presents information about hereditary predisposition to cancer for the general public.

HUNGARY

Education of Oncogenetic is briefly included in the subjects of either Oncology or Clinical Genetic for undergraduate courses of Medical Universities. It would be important to strengthen the ongogenetic training not only at the level of undergraduate studies but also for postgraduate level too.

There is a need to organize a good training program for Oncologycal license exam with oncogenetic specifities or Clinical Genetic Board Exam with special oncogenetic training.

7. Identification of the practical need (infrastructure, human, and financial resources) for establishing and developing an Oncogenetic Network at the level of each country involved as a partner in the HOPE project.

The oncogenetic approach of CRC involves 3 dimensions of the activity within an Oncogenetics Department: clinical for subjects monitoring; molecular for laboratory investigation, and epidemiological for statistical analysis and the interpretation of all data.

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For these activities there are many important needs that have to be considered:

a. ***infrastructure*** – Oncogenetic Centers/ Departtments;
b. ***human resources*** – trained doctors and nurses from different specialties, and statisticians/ informatician that will help the Department/ Center with the management of the computer network, software and other IT issues - needed to acquire the necessary information and to build the local, interregional and national network of Oncogenetics;
c. ***Multidisciplinary Consultancy Group of specialists:*** epidemiologists, oncologists, geneticists, gastroenterologists, gynecologists, surgical oncologists, family doctors, imaging specialists, psychiatrists, specialists in bioethics, biologists, and psychologists;
d. ***cost-efficiency approach***: taken into account for the evaluation of one individual: the cost of clinical and epidemiological investigation for a person which was diagnosed with a genetic risk for CRC; the cost for molecular tests for gene mutation identification for a person which was investigated through; and the cost for the investigation using clinical, epidemiological, and molecular methods of a relative of a person diagnosed with a risk for CRC;
e. ***patient education and counselling***: including the informed consent, the oncogenetic counselling, and the result communication;
f. ***appropriate local and national strategies***.

Table XVI

Identification of the practical need for establishing and developing an Oncogenetic Network at the level of each country involved as a partner in the HOPE project

Country / Needs	**FRANCE**	**ROMANIA**	**HUNGARY**	**BULGARY**
Infrastructure		**- Department of Oncogenetic – UMF Iasi** - **ONCOGEN – Centre for Gene and Cellular Therapies in the**	- **NEED** for molecular testing of genetic risk factors (BRCA1, BRCA2, MMR, APC etc).	Oncogenetic centers (situated in the medical universities) **NEEDED**

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		Treatment of Cancer (Timisoara) **- NEED for development**		
Human resources		**- Department of Oncogenetic – UMF Iasi** **- NEED for development**	- **NEED** to interpret the results obtained, which will be at the basis of an epidemiological assessment of the risk factors for cancer in the Hungarian population	Trained staff **NEEDED**
Multidisciplinary Consultancy Group of specialists		**- Department of Oncogenetic – UMF Iasi** **- NEED for development**	- The long-term goal **is to generate an oncogenetic expertise** that will connect Hungary to similar European structures designed to monitor patients with hereditary cancer risk.	Oncogenetic centers will organize training programs for specialists dealing with cancer patients **NEEDED**
Cost-efficiency approach		**- Department of Oncogenetic – UMF Iasi** **- NEED for**		**NEEDED**

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		development		
Patient education and counselling		**- Department of Oncogenetic – UMF Iasi** **- Oncogen – Centre for Gene and Cellular Therapies in the Treatment of Cancer (Timisoara)** **- NEED for development**	- **NEED** to identify and recruit patients with hereditary risk	Oncogenetic centers will organize training programs for ***patients*** at risk for hereditary cancer, ***their families*** and the ***general public*** **NEEDED**
Appropriate local and national strategies		**NEEDED**	- **NEED** for National Strategies for Diagnosis and Oncogenetic management of hereditary cancer patients	**NEEDED**

FRANCE

The development of an Oncogenetic Network between the differents HOPE partners requires human, material and financial needs.

Indeed, the access to very high-throughput sequencing, the increase in the number of indications in oncogenetic, and this for diagnostic or therapeutic purposes, requires additional human resources, which can be based on the creation of a position of doctor geneticist in 0.3 full time.

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