Additional Primary Cancers in Veterans Surviving Colorectal Cancer – A Critical Analysis

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Abstract

Background

There is evidence that colorectal cancer (CRC) survivors in the general population have a higher incidence of additional primary cancer (APC). In addition, distinct patterns of APC have been seen in survivors with right side colon cancer (RCC) versus those with left side colon and rectal cancer (LCRC). These findings may not be representative for veterans surviving colorectal cancer.

Methods

Retrospective chart review was done for 1540 veterans treated for sporadic CRC between July 1995 and December 2011 at three major Veteran Affairs Medical Centers. Sex, war period served, age and pathological stage at diagnosis, tumor laterality, and site/organs of APCs were collected.

Results

99% of our cohort were male. The average age of CRC surviving veterans was 70 as compared to 68 reported in the general population. 27.4% of our cohort had at least one APC as compared to less than 12% reported for the general population. CRC surviving veterans with one or two APCs were older than those without APC (71.2 or 72.5 respectively vs 69.4). The incident of APC was highest in Korean War veterans (27.8%), followed by World War II veterans (24.8%), and Vietnam War veterans (15.9%). Veterans with RCC were older than those with LCRC (71.7 vs 68.8). They also had a higher incidence of APC (32.9% vs 22.9%). This difference remained unchanged after the cohorts were aged matched (32.9% vs 25.5%). There were more Lynch syndrome related APCs in veterans with RCC that veterans with LCRC (9.6% vs 6.4%). However, this difference did not remain statistically significant in the age-matched cohorts.

Conclusion

More than one in four veterans surviving CRC had APC. Veterans with APC were older, more likely to be Korean War or World War II veterans. There were distinct differences between veterans surviving RCC versus LCRC.

Background

With advances in screening and treatments for various common malignancies, the overall cancer mortality in the United States has fallen by 22% between 1991 and 2011 (1). With this improvement in survival, there is a growing population of cancer survivors who face risk of developing additional primary cancers (APCs). Indeed, it has been shown that cancer survivors in the United States, part of Europe, and

Asia have a life-time risk of developing an APC up to 8% (2–4). Among these cancer survivors, colorectal cancer (CRC) survivors carry a significantly higher risk of developing APC as compared to the general population without an oncologic history (5–8). The incident of APC in CRC survivors in the general population ranged from 4.9% in Asia to 11.5% in the United States (8, 10). These increased risks may be due to various factors including genetic syndromes, lifestyle risk factors, and potential delayed effect of chemotherapy and radiotherapy.

While there is ample evidence about the incidence of APC in survivors of general cancer and CRC in the general population, little is known about the incidence of APCs in CRC surviving veterans. Veterans, especially those who receive their care in the Veteran Affair (VA) system, have certain characteristics that could adversely affect their risk of developing malignancy. Homelessness is higher in veterans receiving care at the VA than the general population (11). VA veterans also tend to be older and are at socioeconomical disadvantage as compared to the general population (12). VA veterans also have a higher prevalence of several medical conditions including diabetes, hypertension, heart disease, and mental health conditions (12–15). These adverse features are likely negatively affecting the risks of malignancy in these veterans.

Recent studies have shown distinct differences between right side colon cancer (RCC) and left side colon and rectal cancer (LCRC) (16–22). Embryologic and anatomic differences aside, RCC has been shown to occur in older patients, be highly immunogenic, respond well to immunotherapy, and in stage I and 2, carry a better prognosis. LCRC tends to occur in younger patients, is not highly immunogenic, and responds better to chemotherapy. Sporadic RCC has also been shown to behave similarly to RCC associated with Lynch syndrome (26).

The object of this study is to determine if VA veterans surviving CRC have a higher incidence of APCs as compared to CRC survivors in the general population, and to identify any difference between veterans with and without APC. Additionally, we look to investigate if distinct differences between RCC and LCRC exist in our CRC surviving veteran cohort.

Methods

This study was approved by the Albany Stratton Veteran Affairs Medical Center (VAMC) Institutional Review Board (protocol #545 – 63). It was conducted as a retrospective chart review of 3500 veterans treated for CRC from three major VAMCs between July 1999 and December 2011. To focus mainly on sporadic CRC, CRC surviving veterans with known cancer syndromes or inflammatory bowel diseases were excluded from our study. Complete data were available for 1540 veterans. Variables collected from this cohort include age and pathological stage of the CRC at diagnosis, sex, war period served, tumor laterality, the presence or absence of any APC, and site/organs of APCs. Tumor laterality were determined via review of operative or pathological reports, or clinical notes in the case of advanced stage CRC. Reliable smoking and alcohol use were not uniformly available and thus not collected. Information about

hazard material exposure during service were not readily available for the majority of the cohort and thus not collected.

The primary outcome of the study was the incidence of APC. The secondary outcome was difference between CRC surviving veterans with and without APCs including age, location and frequencies of APCs, and period of war service. Veterans were classified into RCC and LCRC subgroup. Difference in age, incidence and distribution of APCs between these two groups were also determined.

Due to non-normality, difference in age and APC distribution was compared using the Kruschal-Willis test. The RCC and LCRC cohorts were matched by age using the optimal matching method. Data analysis and visualization were performed using the R statistical programming languages and supporting packages including MatchIt, ggplot2 and Plotly.

Results

Complete records were available for 1540 CRC surviving veterans. Table 1 showed the general demographics of the cohort. Only 1% were female. The majority of veterans in the cohort served in World War II (WWII) (36.6%), Korean War (31.8%), or Vietnam War (30.2%). Only 1.3% served in Persian Gulf War (PGW). The average age of the cohort was 70. WWII veterans were the oldest (73.4) while PGW veterans were the youngest (59.1). The distribution of stage I, II, II, and IV was 19.5%, 34.6%, 25.1%, and 20.1% respectively. More than half of the cohort had LCRC (56.4%). The location of the tumor was not known in 4.4% and 1.8% had more than one tumor.

Table 1
Characteristics of the Cohort

		% (n)	Age
Sex	Male	99 (1534)	70
	Female	1 (16)	
Period of War Service	World War II	36.6 (548)	73.4
	Korean War	31.8 (467)	70.4
	Vietnam War	30.2 (452)	66.4
	Persian Gulf War	1.3 (20)	59.1
Anatomic Location	Right	36.8 (566)	71.7
	Left	56.4 (868)	68.8
	Transverse	0.7 (11)	75.2
	Unknown	4.4 (67)	71.6
	Multiple	1.8 (28)	68.9
Pathological Stage	I	19.5 (296)	70.6
	II	34.6 (524)	70.6
	III	25.1 (380)	69.8
	IV	20.1 (305)	69.3

As shown in Table 2, 24% of our cohort had one APC while 3.4% had two or more APCs. The incidence of one APC and two or more APCs is highest in Korean War veterans (27.8% and 3.4%) followed by WWII veterans (24.8% and 3.1%) and Vietnam War veterans (15.9% and 2.2%). The differences in the incidence of APC across the sub groups serving different war periods were not statistically significant. In veterans with RCC, 29% had one APC and 3.1% had more than one APC while only 19.9% of veterans with LCRC had one APC and 2.7% had more than one APC. This difference between the RCC and LCRC subgroup was statistically significant ($p < 0.001$).

Table 2

Incidence of Additional Primary Cancer of the Cohort According to the War Period Service and Anatomical Location

	No Additional Cancer % (n)	One Additional Cancer % (n)	Two or More Additional Cancer % (n)	
Cohort	72.5 (1040)	24 (349)	3.4 (51)	
World War II	72.1 (412)	24.8 (136)	3.1 (17)	p = 0.5416
Korean War	68.8 (324)	27.8 (136)	3.4 (16)	
Vietnam War	81.9 (370)	15.9 (72)	2.2 (10)	
Right Colon	67.9 (380)	29 (160)	3.1 (20)	p < 0.001
Left Colon and Rectum	77.4 (672)	19.9 (170)	2.7 (26)	

To determine if there was any additional significant difference between veterans surviving RCC versus LCRC, we looked at age, type and distribution of APC in these two subgroups (Table 3). As a whole, veterans with more than APCs were statistically older than veterans with only one APC who, in turn were older than their counterparts without APC (72.5, 71.4, and 69.4 respectively). This trend repeated within the RCC and LCRC subgroups (Table 3A). Interestingly, veterans with RCC were statistically significantly older than their LCRC counterparts (71.8 vs 68.7). This difference in age replicated both in RCC and LCRC veterans without APC (71.4 vs 68.1) and in RCC and LCRC with one APC (72.8 vs 70.7) (Table 3A). Table 3B showed the distribution of APC of the whole cohort and of the RCC and the LCRC subgroups. Excluding CRC, the distribution of APCs in the RCC and LCRC subgroups was similar to that in the general cohort, with prostate, lungs and bladder cancers account for more than one third of all APCs. Table 3C showed the incident of all APCs and of Lynch-syndrome related cancers including CRC, kidney, bladder, liver, pancreas, small bowel and stomach cancer in the RCC and LCRC group. Veterans with RCC has a higher rate of APCs than their LCRC cohort (32.9% vs 22.9%). This difference remained intact after we age-matched the two groups (32.9% vs 25.5%). There were more Lynch-syndrome related APCs in unmatched veterans surviving RCC (9.6%) than in unmatched veterans surviving LCRC (6.4%). However, this difference did not persist in the age-matched cohorts (9.6% vs 7%).

Table 3 Incidence of Additional Primary Cancer in Relationship with Sidedness and Age (A), Type of Additional Primary Cancer (B), and Sidedness and Lynch Syndrome-related Cancers (C)

A

Age					
		No Additional Cancer	One Additional Cancer	Two or More Additional Cancers	
Cohort	70	69.4	71.4	72.5	p<0.001
Right Colon	71.8	71.4	72.8	72.6	
Left Colon and Rectum	68.7	68.1	70.7	72.5	

B

	Cohort % (n)	Right Colon % (n)	Left Colon and Rectum % (n)
Colon and Rectum	6.2 (28)		
Prostate	38.4 (173)	41 (82)	36.9 (82)
Lungs	15.3 (69)	14.5 (29)	17.1 (38)
Bladder	11.8 (53)	10 (20)	13.1 (29)
Blood	8.4 (38)	8 (16)	8.6 (19)
Kidney	6.4 (29)	7 (14)	4.5 (10)
Oropharynx and Larynx	6 (27)	5.5 (11)	5.7 (13)
Esophagus	2.9 (13)	2 (4)	4.1 (9)
Melanoma	2.7 (12)	3.5 (7)	1.8 (4)
Pancreas	1.8 (8)	2 (4)	1.8 (4)

C

	Right Colon % (n)	Left Colon and Rectum % (n)	
Cohort	100 (584)	100 (877)	
With Additional Cancer	32.9 (192)	22.9 (201)	p<0.001
With Lynch Related Cancer	9.6 (56)	6.4 (56)	p=0.0312
With Additional Cancer Age-Matched	32.9 (192)	22.5 (149)	p=0.0069
With Lynch Related Cancer Age-Matched	9.6 (56)	7 (41)	p=0.138

Discussion

Our study is the first to look at APC in a large cohort of veterans surviving CRC. To significantly reduce any genetic bias, we excluded all veterans with CRC related to any genetic syndromes such as Lynch or familial adenomatous polyposis, or inflammatory diseases such as Crohn's or ulcerative colitis. We showed that veterans surviving CRC had a very high incident of APC, that veterans with APC differed from those without APC in age and period of war service. We showed distinct difference in age and specific APC distribution between veterans surviving RCC versus LCRC.

Sex distribution in the veteran population has always been male dominant. The national distribution of female veterans 40 or older ranges from 2.4 to 16.4% (13). Our cohort distribution of 1% female skewed heavily toward prostate cancer as one of the major APCs. Our low representation of PGW veterans (1.3%) likely reflected the fact that many of the PGW veterans were not old enough to be at risk for CRC during our study period (1995–2011). Stage distribution of CRC in our cohort was similar to the distribution of 40% localized (I and II), 36% regional (III), and 20% distance (IV) reported in the general population during the period of 2001–2010 (1). Our distribution of 36.8% RCC and 56.4% LCRC was also similar to the distribution of 38% proximal colon and 55% distal colon and rectum seen in male CRC patients in the general population during the same time period. These findings indicated that manifestation of CRC in our veteran cohort is similar to manifestation of CRC seen in the general population.

We found a very high incidence of APCs in veterans surviving CRC with more than one out of four veterans had at least one APC. The rate of APC was statistically different if we grouped our cohort according to the war service, with the highest rate seen in Korean War veterans and the lowest seen in Vietnam War veterans. This difference in APC rate could not be entirely attributed to age since the oldest group was WWII veterans with the second highest rate of APCs. Our finding suggested that each group of veterans could be exposed to hazardous factors unique to their period of war service. It has been showed that CRC survivors in the general population are at higher risks of developing APCs. This risk varies

among various reports ranging from 4.9–11.5% (2–4). Yet, the highest rate of APC in CRC survivor in the general population remains significantly lower than the lowest rate 18.1% seen in Vietnam War veterans. Our findings suggest that veterans face additional occupational hazard that strongly increases their risks of APCs. This occupational hazard is likely war specific and currently not identified or understood.

For men in the general population, the average age at diagnosis of colon and rectal cancer is 68 and 63 respectively (23). The average age of our cohort, the RCC and LCRC subgroup were older (70, 71.8 and 68.7 respectively). This is in keeping with the finding that male veterans are older than their civilian counterparts (12). We found that the oldest subgroup in our cohort were WWII veterans followed by Korean War veterans, Vietnam War veterans, and PGW veterans, consistent with the timeline of these war periods.

We looked at the distribution of APC in our cohort. The ten most common APCs in our cohort are cancer of the prostate (38.4%), lungs (15.3%), bladder (11.8%), blood (8.4%), kidney (6.4%), colon and rectum (6.2%), oral cavity and pharynx (6%), esophagus (2.9%), melanoma (2.7%), and pancreas (1.8%). Both the RCC and the LCRC subgroup had a similar distribution. As a whole and within subgroup, cancer of the prostate, lungs and bladder make up more than two third of all APCs. As comparison, the ten most common APCs in CRC survivors in the United States are cancer of the prostate (20.1%), lungs (18.7%), breast (11.3%), bladder (6.9%), non-Hodgkin lymphoma (4.5%), melanoma (3.5%), kidney (3.3%), endometrium (3.1%), and thyroid (1.4%) (2). Prostate, lungs and bladder cancer remain prominent survivors of CRC in the general population. There is no statistical difference in the trend seen in our cohort as compared to the trend seen in the general population. These findings indicate that the general characteristic of veterans surviving CRC in our cohort is similar to the characteristic seen in CRC survivors in the general population.

There has been ample evidence showing distinct difference between RCC and LCRC in the general population (16–22). We sought to determine if these differences existed in our cohort. In the general population, patients with right colon cancer were older than patients with left colon cancer or rectal cancer (57 vs 53 or 54, respectively) (25). Similarly, we found that our RCC cohort were older than our LCRC cohort (71.7 vs 68.8, p < 0.001). Interestingly, we found that when stratifying by sidedness, our CRC surviving veterans remained consistently older than their civilian cohort (71.7 vs 57 and 68.8 vs 53 or 54, for RCC and LCRC cohort respectively). We also found a significantly higher incidence of APCs in RCC cohort (32.9% vs 22.9%, p < 0.0001). This difference persisted in age-matched RCC and LCRC cohort (32.9% vs 25.5%, p = 0.00678), indicating that older age in the RCC cohort is not responsible for the higher rate of APCs. So far, this finding has not been reported in the literature. Recently, it has been reported that sporadic RCC behaves similarly to RCC associated with Lynch syndrome (26). When we compared the overall incidence of Lynch syndrome-related APCs including additional CRC, cancer of the kidney, bladder, liver, pancreas, small bowel and stomach, we found that veterans with RCC had a higher rate of Lynch syndrome-related APCs as compared to their LCRC cohort.

Our study has several limitations. First, it is a retrospective review of a veteran population in a geographically specific area and may not represent all veterans. Second, several cofounders including alcohol, smoking, obesity, known hazard exposure including Agent Orange and Camp Lejeune exposure were not collected. These confounders are known to increase the risks of developing malignancy. Third, we did not record the temporal sequences of the CRC and the APCs and thus we could not directly link the risks of APC to the index CRC.

Conclusion

Our study is the first one that looked at APCs in a large cohort of veterans with CRC. We showed that while veterans surviving CRC shared many general characteristics with CRC survivors in the general population, veterans surviving CRC had a much higher incidence of APC than CRC survivors in the general population. We showed that APCs occurred at a higher rate in Korean War veterans followed by WWII and Vietnam War veterans. Veterans with APCs were older than veterans without APC. We also showed distinct difference between veterans with RCC and veterans with LCRC supporting the findings of different biology of right colon cancer and left colon cancer and rectal cancer. Our study suggests a need for a more comprehensive study of multiple malignancies in veterans. It also shows a need for heighten vigilance and a more stringent screening for malignancy, especially those who have survived CRC.

Abbreviations

CRC
Colorectal Cancer; APC:Additional primary cancer; RCC:Right colon cancer; LCRC:Left colon and rectal cancer; VA:Veteran Affair; VAMC:Veteran affairs medical center; WWII:World war II; PGW:Persian Gulf war.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Stratton Veteran Affairs Medical Center (VA IRB project # 545063). Informed consent from participants was waived because this was a retrospective chart review and included data collected from deceased patients. Only de-identified information was collected and analyzed.

Consent for publication

Not applicable.

Availability of data and material

The datasets used for the current study are availablefrom the corresponding author on reasonable request.

Authors' contributions

Conception and design: PN, NA, JB, and ML.Data acquisition: ML. Data analysis: PN, NA, JB, and ML. Manuscript drafting: PN, NA, JB, and ML. All authors have read and approved the final manuscript.

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